HCL,
4.1.80
CUK-H03494-D02476

JULY 1979 • VOL. 190, NO.
ISSN 0003-4932 • ANSU.

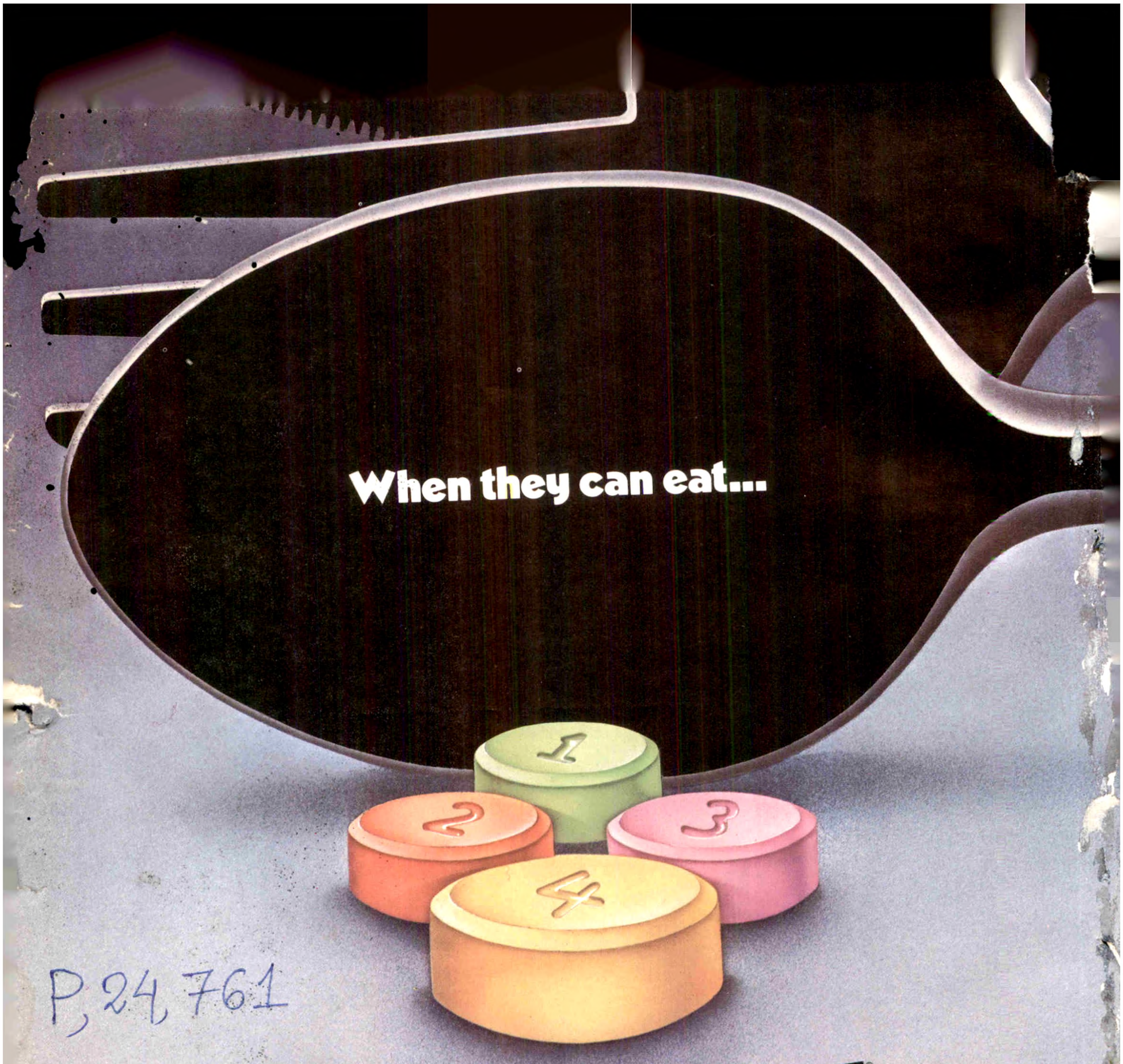
ANNALS of SURGERY

A Monthly Review of
Surgical Science and Practice
Since 1885

24

LIBRARY

J. B. LIPPINCOTT COMPANY
PHILADELPHIA • TORONTO



P, 24, 761

Oral
Dilaudid®
hydromorphone HCl Ⓒ

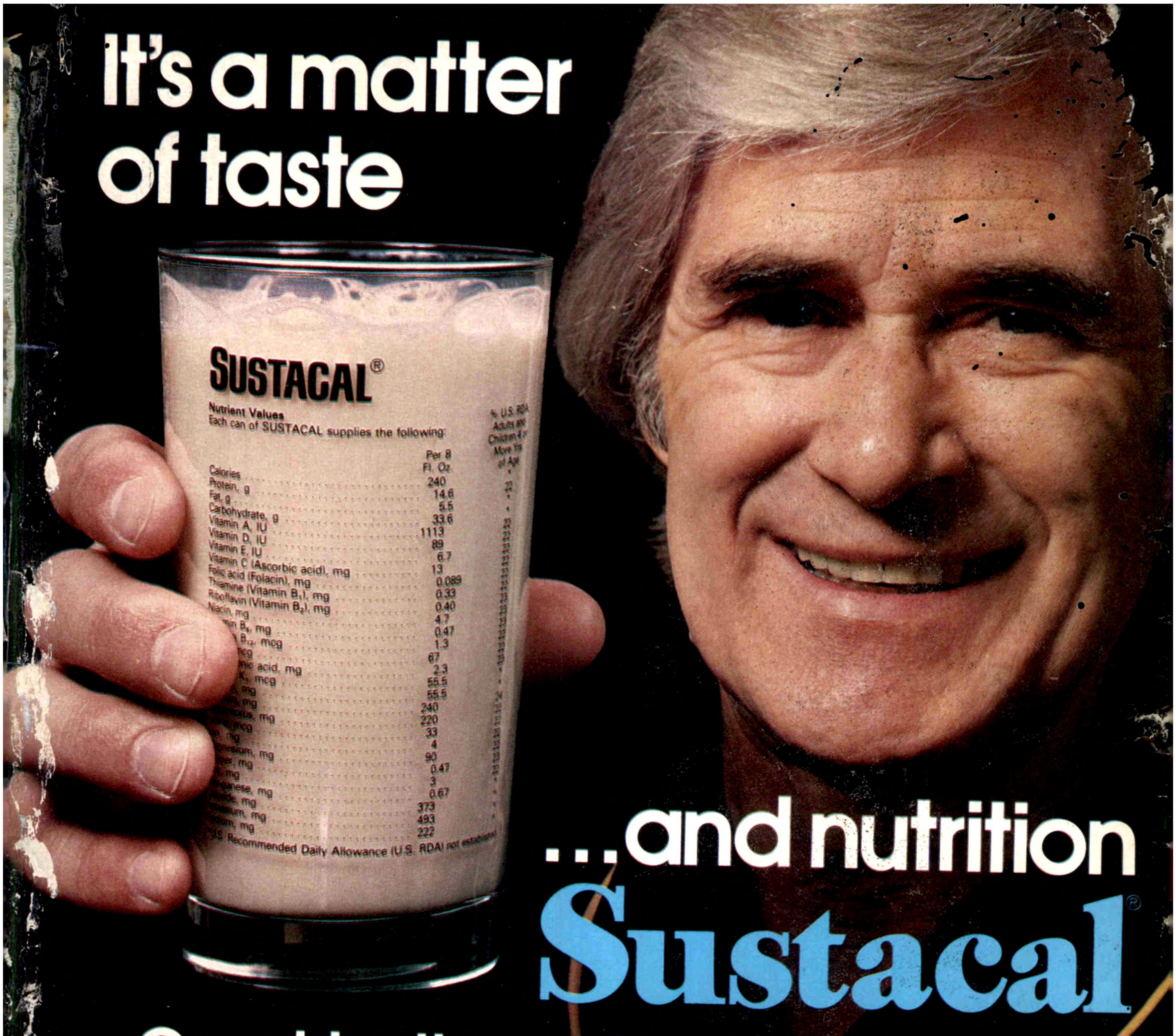
The first step after injectables in post-op analgesia.

Description: Dilaudid is hydromorphone, a hydrogenated ketone of morphine.
Indications: For relief of moderate to severe pain.
Contraindications: Suspected increased intracranial pressure, status asthmaticus.
Warnings: May be habit forming with a potential for addiction equivalent to morphine in equi-analgesic doses. Tolerance may also occur. As with all narcotics, use in early pregnancy only when expected benefits outweigh risks.
Adverse Effects: Nausea, vomiting, diarrhea, constipation, anorexia and somnolence may occur although unlikely with appropriate dose selection.
Dosage and Administration: Dosage must be individualized. The usual adult dose is 2 mg every 4-6 hours, as necessary, for moderate to moderately severe pain. For more severe pain, 3-4 mg or more every 4-6 hours, as necessary, may be required.
Treatment of Overdosage: If overdosage is treated within an hour, emesis and gastric lavage should be attempted. Special attention should be given to respiration and, if depression occurs, it may be antagonized by the use of naloxone hydrochloride (Narcan®)—Endo, nalorphine hydrochloride (Nalline®)—Merck Sharp & Dohme or levallorphan tartrate (Lorfan®)—Roche, as recommended by the manufacturer. Other supportive measures should be applied when indicated.
How Supplied: Dilaudid HCl color coded tablets (NOT FOR INJECTION) imprinted with K logo on one side and potency on other side as follows: green— mg; orange—2 mg; pink—3 mg and yellow—4 mg. Available in: 1 mg—bottles of 100 (NDC #0044-10 02), 2 mg—bottles of 100 (NDC #0044-1022-02) a 500 (NDC #0044-1022-03), 3 mg—bottles of (NDC #0044-1023-02), 4 mg—bottles of 100 (N #0044-1024-02) and 500 (NDC #0044-1024-03).

Knoll Pharmaceutical Company
Whippany, New Jersey 07981

Member Company, Certified Medical Representative Institute, Inc.

It's a matter of taste


SUSTACAL®
Nutrient Values
Each can of SUSTACAL supplies the following:
Per 8 Fl. Oz.
% U.S. RDA Adults and Children 4 or More Yrs of Age
Calories 240
Protein, g 14.6
Fat, g 5.5
Carbohydrate, g 33.6
Vitamin A, IU 1113
Vitamin D, IU 89
Vitamin E, IU 6.7
Vitamin C (Ascorbic acid), mg 13
Folic acid (Folacin), mg 0.089
Thiamine (Vitamin B1), mg 0.33
Riboflavin (Vitamin B2), mg 0.40
Niacin, mg 4.7
U.S. Recommended Daily Allowance (U.S. RDA) not established

...and nutrition Sustacal®

Great tasting nutritional support in a small, easily-consumed serving.

When surgery, therapy or disease reduces your patients' appetites or increases their needs, they need a nutritional boost. They need Sustacal.

Sustacal is a great-tasting nutritional supplement that helps insure daily nutritional needs are met — without replacing the foods patients are eating.

Sustacal is a delicious way to give your patients well-balanced nutrition in a small, easily-consumed serving . . . a maximum amount of nutrition in a minimum volume.

Sustacal comes in a variety of flavors and forms . . . ready-to-use liquid, pudding, and powder that mixes readily with milk.

So, when your patients need extra nutrition, specify Sustacal.

Mead Johnson
NUTRITIONAL DIVISION

Pathogens don't compromise. Why should you?

Just one pathogen species missed by an antiseptic can cause serious problems. That is why scrubbing and prepping leave no room for compromise with the quality of an antiseptic. A small difference in cost is not worth the risk.

Optimal antisepsis you can rely on

BETADINE Microbicides promptly kill gram-positive and gram-negative bacteria, fungi, viruses, protozoa and yeasts.

BETADINE Microbicides have been documented specifically by name—and in the same formulations you employ in practice—in over 650 published reports encompassing thousands of clinical procedures.

BETADINE Microbicides were also chosen by NASA for disinfection procedures in Apollo splashdowns and in the Skylab mission.

BETADINE Microbicides for surgical confidence

____ BETADINE Surgical Scrub*—for surgical scrubbing and patient degerming.

____ BETADINE Solution or BETADINE Aerosol Spray—for patient prepping and postoperative antisepsis on incisions.

Uncompromising antisepsis for scrubbing and prepping

BETADINE® Surgical Scrub
BETADINE® Solution
BETADINE® Aerosol Spray

*In the rare instances of local irritation or sensitivity, discontinue use by the individual.

Purdue Frederick
©Copyright 1979, The Purdue Frederick Company/Norwalk, CT 06856

A9458 214679

Annals of Surgery

A Monthly Review of Surgical Science and Practice

Also the official publication of
THE AMERICAN SURGICAL ASSOCIATION
THE SOUTHERN SURGICAL ASSOCIATION
PHILADELPHIA ACADEMY OF SURGERY
NEW YORK SURGICAL SOCIETY

EDITORIAL AND ADVISORY BOARD

DAVID C. SABISTON, JR., M.D., *Chairman*
Durham, N.C.

J. WESLEY ALEXANDER, M.D.
Cincinnati, O.

WILLIAM A. ALTEMEIER, M.D.
Cincinnati, O.

W. GERALD AUSTEN, M.D.
Boston, Mass.

HENRY T. BAHNSON, M.D.
Pittsburgh, Pa.

WARREN H. COLE, M.D.
Asheville, N.C.

MICHAEL E. DE BAKEY, M.D.
Houston, Tex.

STANLEY J. DUDRICK, M.D.
Houston, Tex.

J. ENGLEBERT DUNPHY, M.D.
San Francisco, Calif.

PAUL A. EBERT, M.D.
San Francisco, Calif.

ERIC W. FONKALSRUD, M.D.
Los Angeles, Calif.

FRANK L. A. GERBODE, M.D.
San Francisco, Calif.

FRANK GLENN, M.D.
New York, N.Y.

FRASER N. GURD, M.D.
Ottawa, Canada

OLGA M. JONASSON, M.D.
Chicago, Ill.

WILLIAM P. LONGMIRE, JR., M.D.
Los Angeles, Calif.

LEONARD D. MILLER, M.D.
Philadelphia, Pa.

FRANCIS D. MOORE, M.D.
Boston, Mass.

WILLIAM H. MULLER, JR., M.D.
Charlottesville, Va.

JOHN S. NAJARIAN, M.D.
Minneapolis, Minn.

JONATHAN E. RHOADS, M.D.
Philadelphia, Pa.

PAUL S. RUSSELL, M.D.
Boston, Mass.

JOHN A. SCHILLING, M.D.
Seattle, Wash.

G. THOMAS SHIRES, M.D.
New York, N.Y.

HARRIS B. SHUMACKER, JR., M.D.
Indianapolis, Ind.

DAVID B. SKINNER, M.D.
Chicago, Ill.

FRANK C. SPENCER, M.D.
New York, N.Y.

SAMUEL A. WELLS, JR., M.D.
Durham, N.C.

Emeritus Members

William F. Rienhoff, Jr., Baltimore, Md., John D. Stewart, M.D., Boca Raton, Fla.

E OF MEDICINE
LIBRARY

J. B. LIPPINCOTT COMPANY, *Publishers*
Philadelphia and Toronto

Annals of Surgery (ISSN 0003-4932) is published monthly for $29.00 per year for the United States and its possessions; resident rate (U.S. only) $21.00; all other countries $39.00; by J. B. Lippincott Co., East Washington Square, Philadelphia, PA 19105. Second-class postage paid at Philadelphia, PA and at additional mailing offices.
POSTMASTER: Send address changes to Annals of Surgery, J. B. Lippincott Co.,
East Washington Square, Philadelphia, PA.
Single copies $5.00. Copyright © 1979 J. B. Lippincott Co. Printed in U.S.A.

Bacteroides

may be implicated in a number of clinical situations, including . . .

- septic abortions
- deep wounds
- bacteremia
- metastatic or other abscesses in association with thromboembolic phenomena

Sensitivity testing is always recommended prior to instituting therapy with Chloromycetin (chloramphenicol). However, in some situations, it may be necessary to administer Chloromycetin before sensitivity tests have been completed.

Bacteroides are the most prevalent microbial flora of man. They are anaerobic, aero-intolerant, nonsporeforming, nonmotile, gram-negative bacilli. They most often appear in mixed infections, and are highly opportunistic. Further, they are very difficult to culture.

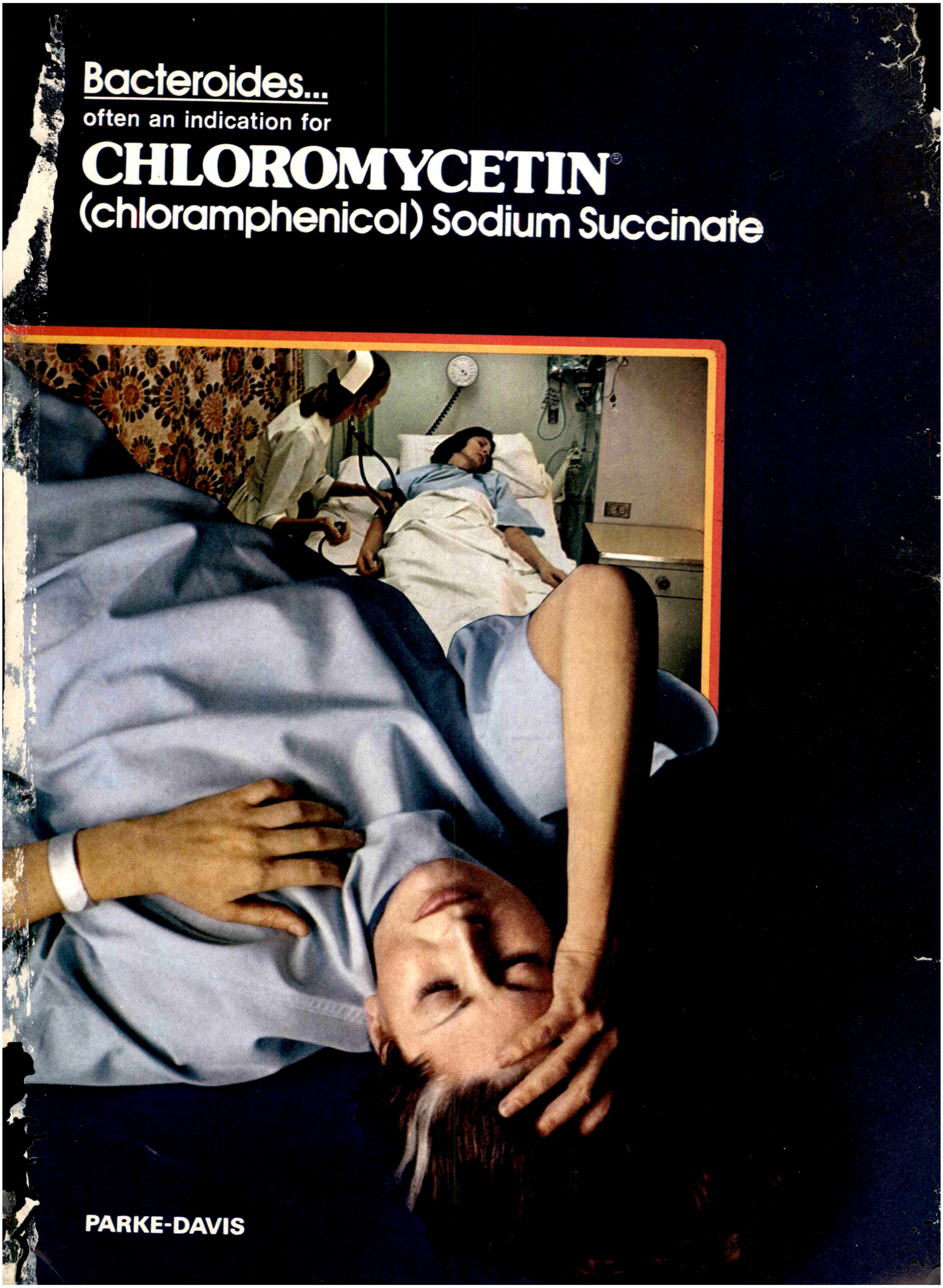
Under normal conditions, bacteroides are benign. But in infectious situations they can be extremely virulent.

Fortunately, most bacteroides infections are susceptible to Chloromycetin (chloramphenicol) therapy. Yet, all too often their presence goes undetected. So today, many authorities recommend early—and vigorous—treatment with Chloromycetin when the clinical impression suggests that a *Bacteroides* infection is present.

Chloromycetin must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated.

But when bacteroides are implicated, Chloromycetin (chloramphenicol) therapy may well be the conservative course. For, in such situations, the benefits-to-risk ratio with Chloromycetin is very favorable.

See next page for full prescribing information.


Bacteroides...
often an indication for
CHLOROMYCETIN®
(chloramphenicol) Sodium Succinate
PARKE-DAVIS

Prescribing information—Chloromycetin
(chloramphenicol) Sodium Succinate
For intravenous administration

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the Indications section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

CHLORAMPHENICOL SODIUM SUCCINATE IS INTENDED FOR INTRAVENOUS USE ONLY. IT HAS BEEN DEMONSTRATED TO BE INEFFECTIVE WHEN GIVEN INTRAMUSCULARLY.

1. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously.
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for,* serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see Indications section).

Each gram (10 ml of a 10% solution) of chloramphenicol sodium succinate contains approximately 52 mg (2.25 mEq) of sodium.

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group, and *Vibrio cholerae.* It is particularly active against *Salmonella typhi* and *Hemophilus influenzae.* The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every six hours for eight doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/ml one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/ml after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/ml over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8% to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/ml in patients receiving divided doses of 50 mg/kg/day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

In accord with the concepts in the Warning Box and this Indications section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present; *in vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by *in vitro* studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in the Warning Box above.

1. Acute infections caused by *S typhi**

   It is not recommended for the routine treatment of the typhoid carrier state.

2. Serious infections caused by susceptible strains in accordance with the concepts expressed above.

   a) *Salmonella* species

   b) *H influenzae,* specifically meningeal infections

   c) Rickettsia

   d) Lymphogranuloma-psittacosis group

   e) Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections

   f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents

3. Cystic fibrosis regimens

---

*In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.*

PRECAUTIONS

1. Base line blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.

3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.

5. There are no studies to establish the safety of this drug in pregnancy.

6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).

7. Precaution should be used in therapy of premature and full-term infants to avoid gray syndrome toxicity. (See Adverse Reactions.) Serum drug levels should be carefully followed during therapy of the newborn infant.

8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose-related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes, and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding (1) the size of the population at risk, (2) the total number of drug-associated dyscrasias, and (3) the total number of nondrug-associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the gray syndrome. One case of gray syndrome has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month-old infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

a) In most cases, therapy with chloramphenicol had been instituted within the first 48 hours of life.

b) Symptoms first appeared after three to four days of continued treatment with high doses of chloramphenicol.

c) The symptoms appeared in the following order:
   (1) abdominal distension with or without emesis;
   (2) progressive pallid cyanosis;
   (3) vasomotor collapse, frequently accompanied by irregular respiration;
   (4) death within a few hours of onset of these symptoms.

d) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.

e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/ml after repeated doses).

f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the intravenous form because adequate blood levels are achieved with chloramphenicol by mouth.

The following method of administration is recommended:

Intravenously as a 10% (100 mg/ml) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 ml of an aqueous diluent such as water for injection or 5% dextrose injection.

DOSAGE

Adults

Adults should receive 50 mg/kg/day in divided doses at six-hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg/kg/day divided into four doses at six-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (eg, bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants

(See section titled Gray Syndrome under Adverse Reactions.)

A total of 25 mg/kg/day in four equal doses at six-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into four doses at six-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

HOW SUPPLIED

NDC 0071-1089-10 (Steri-Vial® No. 57)

Chloromycetin (chloramphenicol) Sodium Succinate is supplied as a dried powder in Steri-Vials (rubber-diaphragm-capped vials). When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per milliliter (1 g/10 ml). Available in packages of 10 vials.

CHLOROMYCETIN, brand of chloramphenicol. Reg US Pat Off
RJ

PD-JA-1280-2-P (2-75)

PARKE-DAVIS, Division of Warner-Lambert Company, Morris Plains, NJ 07950

ANNALS OF SURGERY

Vol. 190 July 1979 No.

CONTENTS

1 **Anastomotic Ulceration Following Subtotal and Total Pancreatectomy**
Clive S. Grant, M.D., *Jonathan A. Van Heerden,* M.B., *Rochester, Minnesota*

6 **Sensitivity of the Canine Pancreatic Intraductal Pressure to Subclinical Reduction in Cholinesterase Activity**
T. D. Dressel, M.D., *R. L. Goodale, Jr.,* M.D., *D. B. Hunninghake,* M.D., *J. W. Borner, Minneapolis, Minnesota*

13 **Protease Inhibitors and Experimental Acute Hemorrhagic Pancreatitis**
Tadao Manabe, M.D., *Michael L. Steer,* M.D., *Boston, Massachusetts*

18 **Infusion of the Branched Chain Amino Acids in Postoperative Patients: Anticatabolic Properties**
Herbert Freund, M.D., *Herbert C. Hoover, Jr.,* M.D., *Susan Atamian,* R.N., *Josef E. Fischer,* M.D., *Boston, Massachusetts*

24 **Use of Doppler Ultrasound in Intraoperative Localization of Intestinal Arteriovenous Malformation**
Marc Cooperman, M.D., *Edward W. Martin, Jr.,* M.D., *William E. Evans,* M.D., *Larry C. Carey,* M.D., *Columbus, Ohio*

27 **The Effects of Metoclopramide on Postoperative Ileus: A Randomized Double-blind Study**
Eugene D. Davidson, M.D., *Theodore Hersh,* M.D., *Richard A. Brinner,* M.D., *Stephen M. Barnett,* M.D., *Lawrence P. Boyle,* M.D., *Atlanta, Georgia*

31 **Typhoid Perforation of the Bowel: Experiences in 78 Cases**
F. C. Eggleston, M.D., *B. Santoshi,* M.S., *C. M. Singh,* M.S., *Punjab, India*

36 **Initial Treatment of Sigmoid Volvulous by Colonoscopy**
James R. Starling, M.D., *Madison, Wisconsin*

40 **Megacolon in the Elderly: Ischemic or Inflammatory?**
Irving B. Margolis, M.D., *Richard S. Faro,* M.D., *Earl M. Howells,* M.D., *Claude H. Organ, Jr.,* M.D., *Omaha, Nebraska*

45 **Evaluation and Complications of 107 Staging Laparotomies for Hodgkin's Disease**
Bernard J. Urlaub, M.D., *Eberhard Mack,* M.D., *Madison, Wisconsin*

48 **Regeneration of Human Liver After Hepatic Lobectomy Studied by Repeated Liver Scanning and Repeated Needle Biopsy**
Tien-Yu Lin, M.D., *Chue-Shue Lee,* M.D., *Chiou-Chiang Chen,* M.D., *Kuong-Yi Liau,* M.D., *Wen-Shih-Jen Lin,* M.D., *Taiwan, R.O.C.*

54 **Five Year Study of Tissue Reaction to Synthetic Sutures**
R. W. Postlethwait, M.D., *Durham, North Carolina*

Now...enteral hyperalimentation by special delivery.

No pumps
Allows continuous gravity-flow administration.

Lightweight
Ambulatory patients can maneuver with more ease.

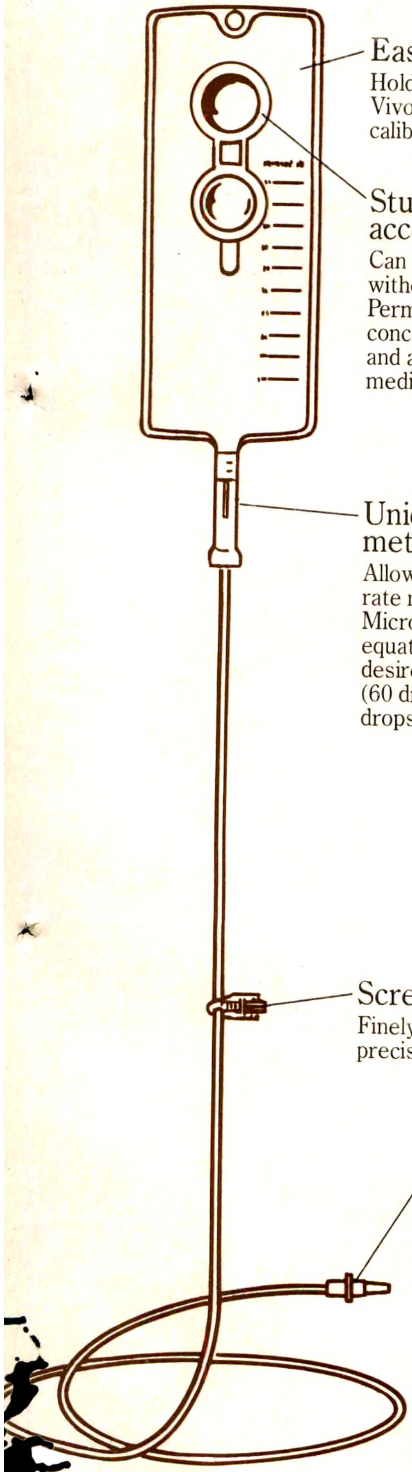
Eliminates jerry-rigging
A single component that's disposable. Saves time for the entire staff.

Economical
Just add Vivonex HN and a feeding tube.

Simple flow regulation

"The plastic bag administration set and a microdrip chamber permit accurate administration during a wide range of rates. The elimination of the need for an infusion pump renders the technique less expensive and cumbersome. The patients may be fully ambulatory while receiving therapy."[1]

Special... because it's a complete system.



Easy-to-fill pouch
Holds up to 1 liter of Vivonex HN; 100-ml calibrations add accuracy.

Sturdy pouch access
Can be opened and closed without weakening. Permits volume or concentration changes and addition of vitamins or medications.

Unique drip meter
Allows simple flow-rate monitoring. Microdrops/minute equate to ml/hr for desired flow rate (60 drops≈1 ml; 60 drops/min≈60 ml/hr).

Screw clamp
Finely threaded for precise adjustment.

Male Luer
Fits most small-caliber feeding tubes.

Special... because it delivers Vivonex® HN.*

VIVONEX HN provides complete enteral nutrition with free amino acids. Being truly elemental, it requires minimal digestion and allows maximal absorption. The extremely low viscosity allows Vivonex HN to flow continuously, at *any* rate, without clogging.

"Increasingly, these diets are used in patients with fistulas, inflammatory bowel disease, partial obstruction, and malabsorption—states for which total parenteral nutrition was once considered most appropriate."[2]

VIVONEX HN—*the only elemental high nitrogen diet*—has "...a nitrogen to calorie ratio of 1:150—the best ratio for anabolism."[3] By continuous administration of Vivonex HN via the Vivonex Delivery System, the same positive nitrogen balance, weight gain, and accelerated wound healing can be achieved as with parenteral hyperalimentation, but without the catheter-induced thrombophlebitis, sepsis, and patient discomfort.

*Information on Vivonex HN usage and precautions accompanies the product and should be reviewed before use.

Norwich-Eaton Pharmaceuticals
Division of Morton-Norwich Products, Inc.
Norwich, NY 13815

VIVONEX®

DELIVERY SYSTEM

References: 1. Page CP, Ryan JA Jr, Haff RC: Continual catheter administration of an elemental diet. *Surg Gynecol Obstet* 142:184-188, 1976. *2.* Randall HT (ed): Nutrition and surgical patients. *Contemp Surg* 11(1):7-22, 1977. *3.* Blackburn GL, Bistrian BR: Nutritional care of the injured and/or septic patient. *Surg Clin North Am* 56:1195-1224, 1976.

EV-8061

CONTENTS *Continued*

58 **Carcinoid Tumors of the Appendix: Mesoappendiceal Extension and Nodal Metastases**
Donald C. Syracuse, M.D., *Karl H. Perzin,* M.D., *John B. Price,* M.D., *Philip D. Wiedel,* M.D., *Ricardo Mesa-Tejada,* M.D., *New York, New York*

64 **The Undescended "Parathymus": An Occasional Cause of Failed Neck Exploration for Hyperparathyroidism**
Anthony J. Edis, M.D., *Don C. Purnell,* M.D., *Jonathan A. Van Heerden,* M.B., *Rochester, Minnesota*

69 **Comparison of Estrogen Receptor Levels in Primary and Regional Metastatic Carcinoma of the Breast**
J. L. Hoehn, M.D., *E. D. Plotka,* PH.D., *K. B. Dickson,* M.D., *Marshfield, Wisconsin*

72 **Nondialysis Uses for Vascular Access Procedures**
Alexander M. Guba, Jr., M.D., *George J. Collins, Jr.,* M.D., *Norman M. Rich,* M.D., *Louis Kozloff,* M.D., *Paul T. McDonald,* M.D., *Bethesda, Maryland*

75 **An *in Vivo* Evaluation of Microaggregate Blood Filtration During Total Hip Replacement**
Edward L. Snyder, M.D., *Patricia S. Underwood,* M.D., *Morton Spivack,* M.D., *Lawrence DeAngelis,* M.D., *Edward T. Habermann,* M.D., *Bronx, New York*

80 **Anoxic Hypothermic Cardioplegia Compared to Intermittent Anoxic Fibrillatory Cardiac Arrest: Clinical and Metabolic Experience with 1080 Patients**
Steven J. Phillips, M.D., *Robert H. Zeff,* M.D., *Cham Kongtahworn,* M.D., *L. A. Iannone,* M.D., *Thomas M. Brown,* M.D., *David F. Gordon,* M.D., *Des Moines, Iowa*

84 **Seeding Arterial Prostheses with Vascular Endothelium: The Nature of the Lining**
Malcolm B. Herring, M.D., *Russell Dilley,* M.D., *Ralph A. Jersild, Jr.,* PH.D., *Laurence Boxer,* M.D., *Austin Gardner,* M.D., *John Glover,* M.D., *Indianapolis, Indiana*

91 **Hemostasis in Massively Transfused Trauma Patients**
R. B. Counts, C. Haisch, T. L. Simon, N. G. Maxwell, D. M. Heimbach, C. J. Carrico, Seattle, Washington

100 **Preoperative Assessment of Resectability for Carcinoma of the Thoracic Esophagus: Part I. Esophagogram and Azygogram**
Shozo Mori, M.D., *Morio Kasai,* M.D., *Toshio Watanabe,* M.D., *Issei Shibuya,* M.D., *Sendai, Japan*

106 **The Effects of Hypothermia on Myocardial Oxygen Consumption and Transmural Coronary Blood Flow in the Potassium-arrested Heart**
W. Randolph Chitwood, Jr., M.D., *James D. Sink,* M.D., *Ronald C. Hill,* M.D., *Andrew S. Wechsler,* M.D., *David C. Sabiston, Jr.,* M.D., *Durham, North Carolina*

117 **Influence of Increasing Carbohydrate Intake on Glucose Kinetics in Injured Patients**
David H. Elwyn, PH.D., *John M. Kinney,* M.D., *Malayappa Jeevanandam,* PH.D., *Frank E. Gump,* M.D., *John R. Broell,* M.S., *New York, New York*

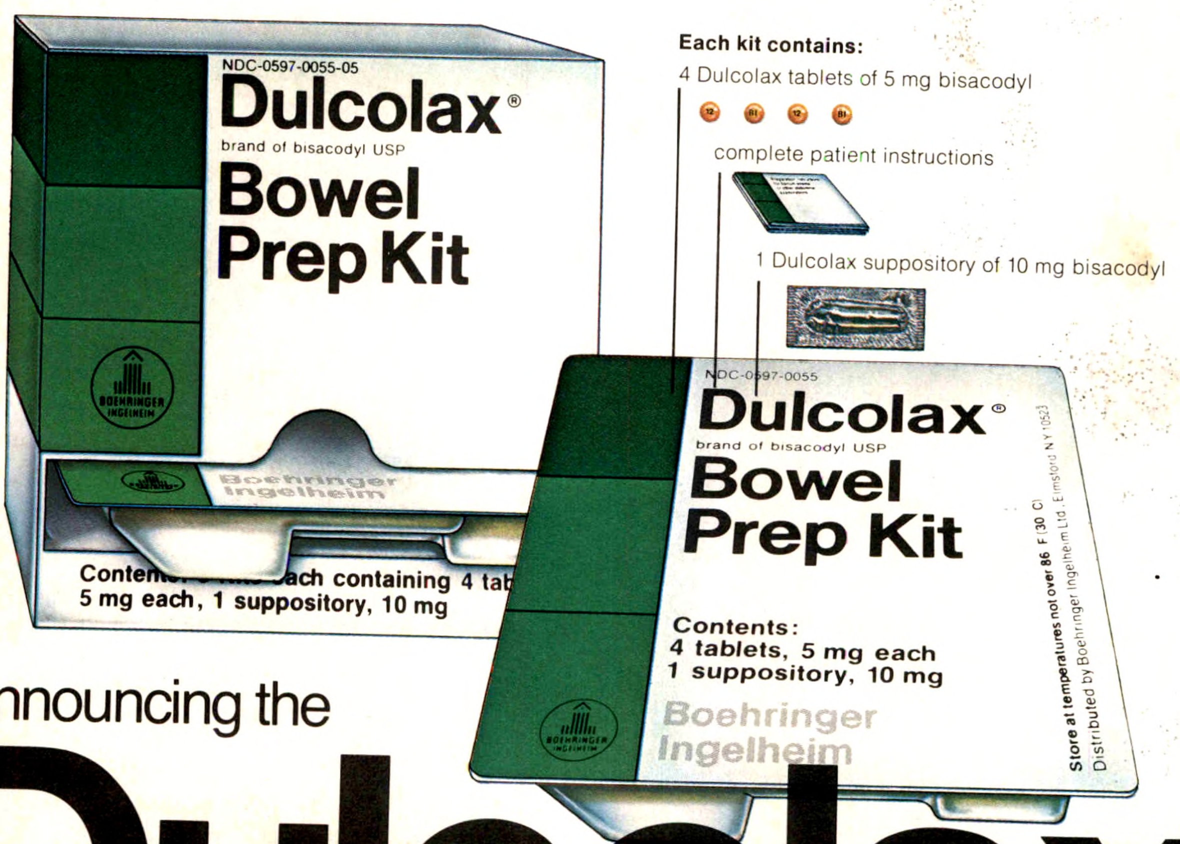
128 **Book Reviews**

- **Compact...**easy to store...all in a sealed, plastic container
- **Versatile...**easily snaps onto the top of a magnesium citrate bottle...can be used with other saline cathartics or with castor oil
- **Economical...**suggested retail price is less than most other kits
- **Convenient...**for nursing staff or the out-patient. Sold in a handy dispenser of 5.

With the Dulcolax Bowel Prep Kit plus magnesium citrate "...the reexamination rate of patients because of poorly cleansed colons has fallen to approximately 1 percent of all barium enema studies."[1]

[1] Sorrentino A P et al. Am J Hosp Pharm *26*:432-435, 1969.

Boehringer Ingelheim Ltd.
Ridgefield, CT 06877



Each kit contains:

4 Dulcolax tablets of 5 mg bisacodyl

complete patient instructions

1 Dulcolax suppository of 10 mg bisacodyl

Announcing the

Dulcolax® Bowel Prep Kit

Notice to Contributors and Subscribers

Annals of Surgery is a monthly journal which considers for publication original articles in the field of surgery. It is the oldest continuously published journal in the English language solely devoted to the surgical sciences. The Editorial Board considers only papers judged to offer significant contributions to the advancement of surgical knowledge.

Contributions. Four typed copies of the manuscript and four copies of the illustrations should be sent prepaid to the Chairman of the Editorial Board of Annals of Surgery:

David C. Sabiston, Jr., M.D.
Annals of Surgery
Department of Surgery
Duke University Medical Center
Durham, North Carolina 27710

Manuscripts and references should be typed double spaced on one side of 8½ × 11 paper leaving wide margins. Authors should retain a complete copy of the manuscript including illustrations in the event that the manuscripts are lost in the mail. A complete address for reprint requests should be included on the title page together with the name of the institution from which the work is being published.

An abstract of *not more than 200 words* should be placed at the beginning of the manuscript. It should accurately reflect the paper and provide readers with a reliable impression of the contents and conclusions of the work.

Digits one to ten should be spelled out, except when used for units of measurement (time, weight, volume, dosage, degrees) percentage, or when decimals are involved; for numbers above ten, numerals should be used. Dorland's Medical Dictionary and Webster's International Dictionary may be used as standard references. Scientific names for drugs should be used when possible. Copyright or trade names of drugs should be capitalized. Units of measurement should be expressed in the metric system. Temperature should be expressed in degrees centigrade. All contributions should be submitted in English.

Black and white illustrations will be reproduced free of charge, but the publisher reserves the right to establish a reasonable limit upon the number supplied. Color illustrations will be published at the author's expense. Black and white photographs should be in the form of glossy prints. Line and wash drawings should be black on white paper, with lettering in black india ink or transfer lettering, large enough to be readable after necessary reduction. Large or bulky illustrations should be accompanied by smaller glossy reproductions of the same. Illustrations should be numbered, the tops indicated, and the author's name and the title of the article in brief appear on the back. A separate typewritten sheet of legends for the illustrations should be supplied.

An alphabetical list of numbered references should appear at the end of the manuscript with corresponding numbers in the text. All references should be specifically mentioned in the body of the manuscript. The list of references should be *selective* with not more than 20 references except under unusual circumstances. References should conform to the style of the Index Medicus.

McNamara, J. J., Molot, M. D. and Stremple, J.: Changes in Some Physical Properties of Stored Blood. Ann. Surg., 174:58, 1971.

PUBLISHER'S NOTICES

Change of Address: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the journal.

Copies will not be replaced without charge unless we receive a request within 60 days of the mailing in the U. S. or within 90 days in all other countries.

Business Address: Subscriptions, reprints, advertising, and all business communications should be addressed to:

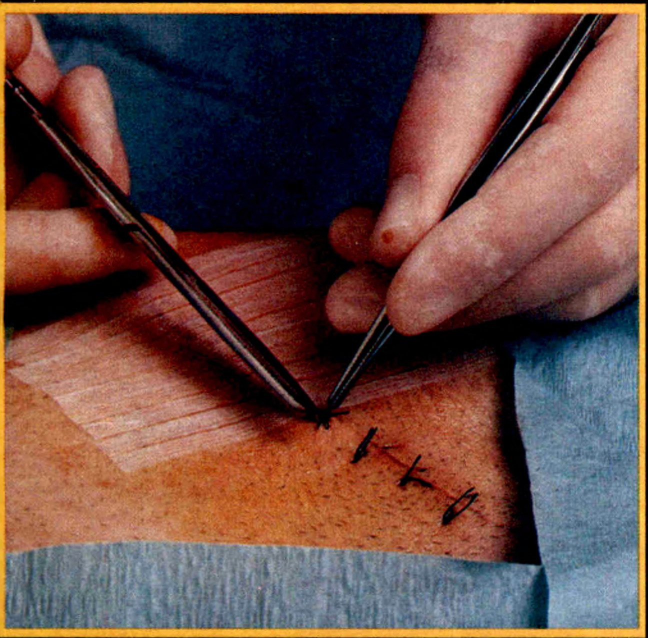
Annals of Surgery
J. B. Lippincott Co.
East Washington Square
Philadelphia, Pa. 19105

Published Monthly. Subscription Rates $27.00 per year in United States and possessions; all other countries $37.00. All prices include postage. Single issues $5.00. Rate for Residents, U.S. only, $19.00.

The publishers accept no responsibility for opinions expressed by contributors.

SUTURE REMOVAL

Remove sutures early and replace with sterile, reinforced STERI-STRIP® Skin Closure for less chance of infection, a finer scar, greater patient comfort.[1]



Sutures removed 72 hours postoperatively.

38 days postop.

Steri-Strip® Skin Closures make suture removal possible at a point that is most beneficial to the wound — 72 hours postoperatively.[2, 3]

The early removal of sutures and replacement with Steri-Strip Skin Closures:

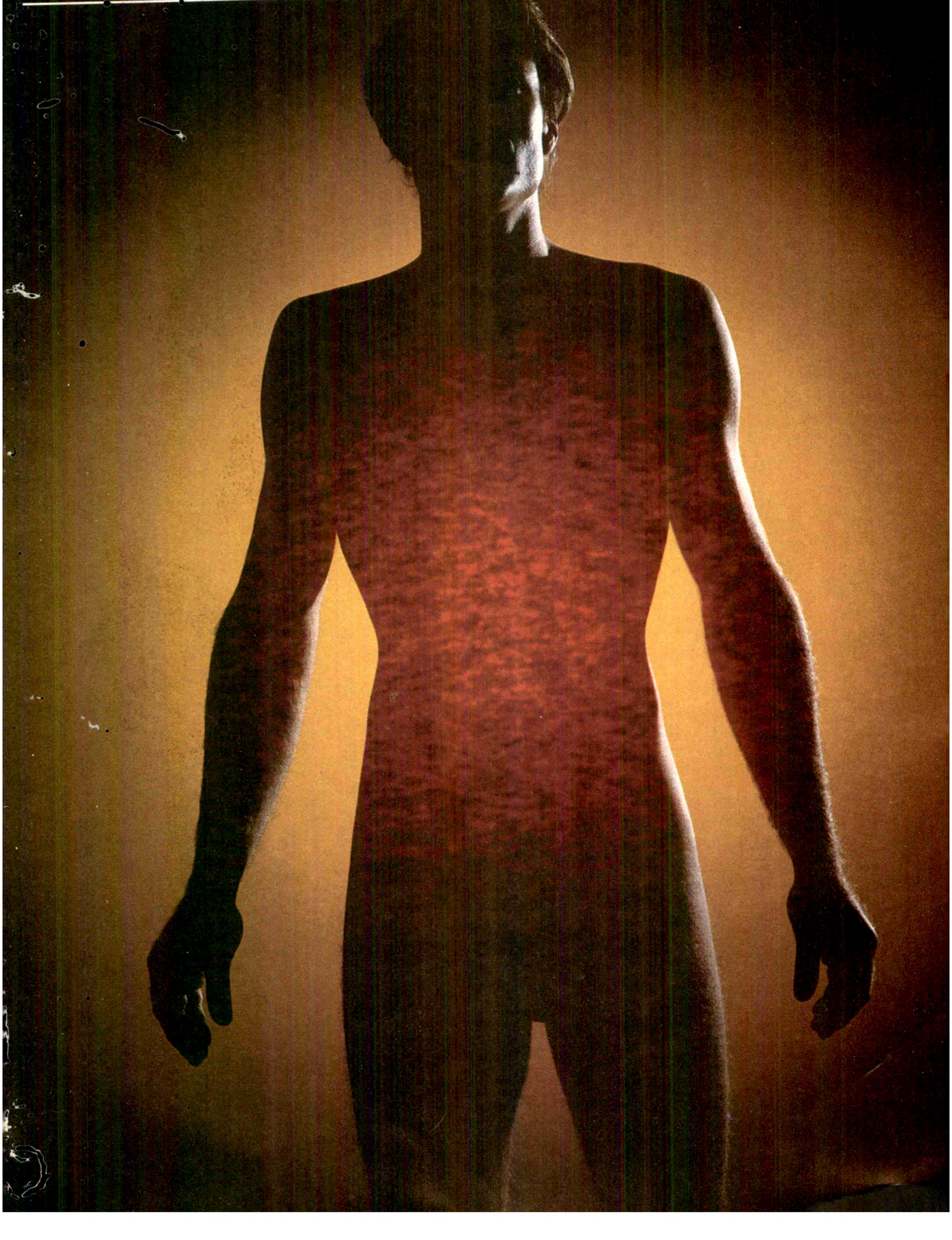
- reduces adverse cosmetic results (needle puncture marks and crosshatching) and produces a finer scar.
- enhances wound healing by enabling the skin to develop tensile strength faster.[4]
- reduces infection potentiation
- provides extended firm wound support
- affords greater patient comfort

Contact your 3M Surgical Products representative for further information. 3M Surgical Products Division, 3M Center, St. Paul, MN 55101.

Surgical Products Division/3M
555-IN, 3M Center
St. Paul, MN 55101
QES-910

REFERENCES:
1. Edlich RF, Rodeheaver G, Kuphal J, deHoll JD, et al: Technique of closu Contaminated wounds. J Am Coll Emer Phys 3:375-381, 1974.
2. Brunius U, Akren Chr: Healing impairment of skin incisions closed with s sutures. Acta Chir Scand 135:369-381, 1969.
3. Lewis JR, Jr: Facial scars resulting from vehicular accidents. Clinics in Plas Surgery 2:143-166, 1975.
4. Forrester JC, Zederfeldt BH, Hayes TL, Hunt TK: Wolff's Law in relation to t healing wound. J Trauma 10:770-779, 1970.

IMPAIRED HOST DEFENSES AND THE GRAM-NEGATIVE THREAT



TICAR®
[Ticarcillin Disodium]

AND CERTAIN AMINOGLYCOSIDES MAY PROVE THERAPEUTICALLY SUPERIOR

BROADER ANTIBACTERIAL COVERAGE

The concomitant use of TICAR and gentamicin or tobramycin provides a wider *in vitro* antimicrobial spectrum than each antibiotic alone* Range includes *Bacteroides* species such as *B. fragilis* and other anaerobic bacteria.

REDUCTION OF MIC'S

TICAR with gentamicin or tobramycin *in vitro* often reduces the Minimum Inhibitory Concentrations (MIC's) of these antibiotics against *Pseudomonas aeruginosa by a factor of 4 or more.*† (An important consideration when aminoglycoside serum levels are similar to the MIC's of the *Pseudomonas* strain.)

EFFICACY IN NEUTROPENIC PATIENTS

TICAR is "...effective regardless of the patient's neutrophil count," while gentamicin and tobramycin are reported to be only minimally effective in neutropenic patients[1]

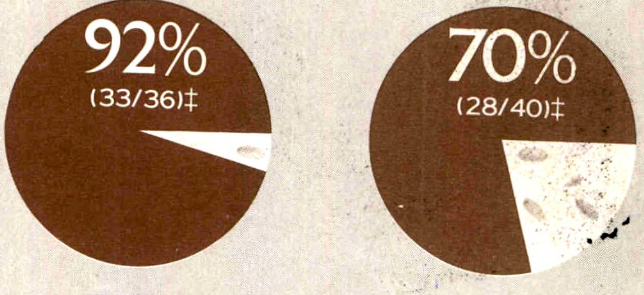
TICAR AND GENTAMICIN OR TOBRAMYCIN: SUPERIOR CLINICAL RESULTS

With Tobramycin:

Patients "...responded more frequently..."[2] when TICAR was used concomitantly with tobramycin:

Clinical Efficacy in Pulmonary Infections Due To *Pseudomonas aeruginosa*

(Adapted from Parry and Neu[2])



TICAR/
Tobramycin

Carbenicillin/
Gentamicin

"The combination of TT [TICAR and tobramycin] appears to be superior to CG [carbenicillin and gentamicin] for the treatment of pulmonary infections due to *Pseudomonas aeruginosa*."[2]

With Gentamicin:

"T + G [TICAR and gentamicin] is an extremely useful initial antimicrobial regimen for empiric therapy of febrile episodes in granulocytopenic cancer patients."[3]

"Ticarcillin is a safe and highly effective parenteral semi-synthetic penicillin..." for serious *Pseudomonas* infections due to susceptible strains[4]

---

*Not all strains are susceptible. *In vitro* susceptibility should not be translated to clinical effectiveness.

†Data on file, Medical Department, Beecham Laboratories.

‡Number of patients responding/total number of patients evaluated.

1. Bodey GP, et al: Management of Bacterial Infections in Cancer Patients. *Chemotherapy.* Reprinted with permission from: Proceedings of the 9th International Congress of Chemotherapy, London, 1975, *1*, Clinical Aspects of Infections.
2. Parry MF, Neu HC: A comparative study of ticarcillin plus tobramycin versus carbenicillin plus gentamicin for the treatment of serious infections due to Gram-negative bacilli. *American Journal of Medicine* 64:961-966, 1978.
3. Murillo J, et al: Comparison of serum bactericidal activity among three antimicrobial combinations. *Antimicrobial Agents and Chemotherapy* 13(6):992-996, 1978.
4. Neu HC, Parry MF: Ticarcillin in serious infections. Read before the Ticarcillin International Symposium, Burgenstock, Switzerland, September, 1977.

Please see brief summary of prescribing information on next page.

Beecham
laboratories
BRISTOL, TENNESSEE 37620

TICAR
(Sterile Ticarcillin Disodium)
for Intramuscular or Intravenous Use

For complete prescribing information, consult official package insert.

ACTIONS: Ticarcillin is bactericidal; it is not absorbed orally, therefore, it must be administered intravenously or intramuscularly.

INDICATIONS: TICAR (Ticarcillin Disodium) is indicated for the treatment of the following infections:

Bacterial septicemia†
Skin and soft-tissue infections†
Acute and chronic respiratory tract infections†‡
†caused by susceptible strains of *Pseudomonas aeruginosa*, *Proteus* species (both indole-positive and indole-negative) and *Escherichia coli*.
‡(Though clinical improvement has been shown, bacteriological cures cannot be expected in patients with chronic respiratory disease or cystic fibrosis.)
Genitourinary tract infections (complicated and uncomplicated) due to susceptible strains of *Pseudomonas aeruginosa*, *Proteus* species (both indole-positive and indole-negative), *Escherichia coli*, *Enterobacter* and *Streptococcus faecalis* (enterococcus).

Ticarcillin is also indicated in the treatment of the following infections due to susceptible anaerobic bacteria:

(1) Bacterial septicemia.
(2) Lower respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess.
(3) Intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract).
(4) Infections of the female pelvis and genital tract such as endometritis, pelvic inflammatory disease; pelvic abscess and salpingitis.
(5) Skin and soft-tissue infections.

Although Ticarcillin is primarily indicated against Gram-negative infections, its *in vitro* activity against Gram-positive organisms should be considered in treating infections caused by both Gram-negative and Gram-positive organisms.

Based on the *in vitro* synergism between Ticarcillin and gentamicin sulfate or tobramycin sulfate against certain strains of *Pseudomonas aeruginosa*, combined therapy has been successful, using full therapeutic dosages.

Culturing and susceptibility testing should be performed initially and during treatment.

CONTRAINDICATIONS: A history of allergic reaction to any of the penicillins is a contraindication.

WARNINGS: Anaphylaxis may occur, especially in patients with an allergic diathesis. Check for a history of allergy to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, the drug should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to Ticarcillin therapy. Serious anaphylactic reactions require immediate emergency treatment with epinephrine, oxygen, intravenous steroids and airway management.

Some patients receiving high doses of Ticarcillin may develop hemorrhagic manifestations associated with abnormalities of coagulation tests. Patients with renal impairment, in whom excretion of Ticarcillin is delayed, should be observed for bleeding manifestations. Such patients should be dosed strictly according to recommendations. If bleeding manifestations appear, Ticarcillin treatment should be discontinued and, if necessary, appropriate therapy instituted.

PRECAUTIONS: During prolonged treatment, periodic checking for organ system dysfunction (renal, hepatic and hematopoietic) is advisable. If overgrowth of resistant organisms occurs, the appropriate therapy should be initiated.

Since the theoretical sodium content is 5.2 milliequivalents (120 mg) per gram of Ticarcillin, electrolyte and cardiac status should be monitored carefully.

In a few patients receiving intravenous Ticarcillin, hypokalemia has been reported. Serum potassium should be measured periodically.

USAGE DURING PREGNANCY: Reproduction studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the fetus due to Ticarcillin. There are no well-controlled studies in pregnant women, but investigational experience does not include any positive evidence of adverse effects on the fetus. Although there is no clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the fetus. Ticarcillin should be used in pregnant women only when clearly needed.

ADVERSE REACTIONS: The following adverse reactions may occur: skin rashes, pruritus, urticaria, drug fever, nausea, vomiting, anemia, thrombocytopenia, leukopenia, neutropenia, eosinophilia. SGOT and SGPT elevations have been reported. Patients, especially those with impaired renal function, may experience convulsions or neuromuscular excitability when very high doses of the drug are administered.

Local reactions at the site of injection have been reported. Vein irritation and phlebitis can occur, particularly when undiluted solution is directly injected into the vein.

DOSAGE AND ADMINISTRATION: Usual adult recommended dosage in bacterial septicemia, respiratory tract infections, skin and soft-tissue infections, intra-abdominal infections and infections of the female pelvis and genital tract, is 3 grams by intravenous infusion every 3, 4 or 6 hours depending on weight and severity of infection; in uncomplicated urinary tract infections, 1 gram I.M. or direct I.V. q.i.d.; in complicated urinary tract infections, 3 grams q.i.d. by I.V. infusion.

Please consult official package insert for details on dosages for patients with renal insufficiency, children, neonates and directions for use.

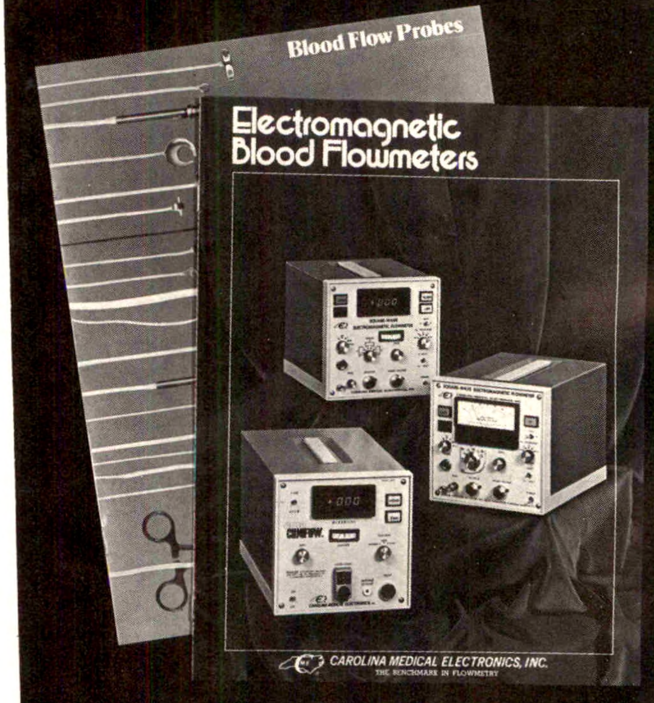
Supplied:
1 Gm, 3 Gm and 6 Gm Standard Vials
3 Gm and 6 Gm Piggyback Bottles

Beecham
laboratories
BRISTOL TENNESSEE 37620

Electromagnetic Blood Flowmeters

- Excellent performance in clinical and research applications
- Simple, reliable operation
- Patient protection system
- Zero flow reference
- Convenient readout
- Excellent frequency response
- Low noise — high resolution
- Total system compatibility
- Multiple flow adaptability
- Compact size
- Available with two-channel recorders
- Wide range of blood flow probes available

Write or call for complete information


Blood Flow Probes
Electromagnetic Blood Flowmeters
CAROLINA MEDICAL ELECTRONICS, INC.
THE BENCHMARK IN FLOWMETRY

CME®

CAROLINA MEDICAL ELECTRONICS, INC.
P. O. BOX 307, KING, N. C. 27021 USA
TELEPHONE (919) 983-5132

ANNALS OF SURGERY
Vol. 190 July 1979 No. 1

Anastomotic Ulceration Following Subtotal and Total Pancreatectomy

CLIVE S. GRANT, M.D., JONATHAN A. VAN HEERDEN, M.B., F.R.C.S(C), F.A.C.S.

From the Mayo Clinic and Mayo Foundation,
Rochester, Minnesota

Ulcerogenic potential exists after subtotal gastrectomy, pancreatic resection and separation of the pancreatic and bile ducts from the gastric outlet. Collectively, as with radical pancreatoduodenectomy or total pancreatectomy, a substantial risk of an anastomotic ulcer developing can be expected. To elucidate this, we reviewed the records of 297 patients who had undergone either radical pancreatoduodenectomy (Whipple procedure) or total pancreatectomy. We found that 18 patients (6%) had developed an anastomotic ulcer and that total pancreatectomy was statistically more ulcerogenic than a Whipple procedure. An anastomotic ulcer was a virulent complication; two-thirds of the patients had bleeding, and it was a contributing cause of death in 22% of patients in whom ulcer developed. In patients who have a favorable prognosis, the addition of vagectomy to either procedure should be considered.

DIRECTED TOWARD CURE of duodenal ulcer disease, partial gastrectomy without vagectomy carries a recurrent ulcer risk that ranges from 2 to 36%,[7–10,15,19] usually averaging 4–6%. Partial gastrectomy with gastrojejunostomy is used for reconstruction after radical pancreatoduodenectomy and total pancreatectomy, but only isolated cases of marginal ulceration in this setting have been reported.[4,18,20]

Whenever the quantity of pancreatic secretions is insufficient for the normal digestion of fat in the upper small bowel, gastric acid output increases.[5] Similarly, transplantation of the pancreatic duct away from the gastric outlet is ulcerogenic. Experimentally, this is demonstrated with the Mann-Williamson preparation, and ulcerogenicity became clinically apparent when Roux-en-Y reconstruction without vagectomy was used for duodenal ulcer operations (Fig. 1). Therefore, the ulcerogenic potential exists after subtotal gastrectomy, pancreatic resection, and separation of the pancreatic and bile ducts from the gastric outlet. Collectively, as with radical pancreatoduodenectomy, a substantial risk of an anastomotic ulcer developing can be expected.

To elucidate this, we sought to further characterize the nature of marginal ulceration as it occurs in patients who had undergone either radical pancreatoduodenectomy or total pancreatectomy.

Our Series

The records of 299 patients who had undergone either radical pancreatoduodenectomy (Whipple procedure) or total pancreatectomy from 1960 through 1975 at our institution were reviewed. Two patients with Zollinger-Ellison syndrome were excluded. Of the 297 patients in the study, 169 were males (57%) and 128 were females (43%). A total of 233 Whipple (78%) and 64 total pancreatectomy (22%) operations were performed (Fig. 2). Follow-up data were obtained on all 297 patients. The median age of the group was 59 years, with a range of 21–85 years. Twenty patients had a definite anastomotic ulcer diagnosed on roentgenogram or at endoscopy, operation, or autopsy, in addition to diagnosis at clinical presentation; two of the 20 were patients with the Zollinger-Ellison syndrome and were excluded from the study. Of the other 18 patients with ulcer, seven (11%) had undergone total pancreatectomy and 11 (5%) had had a Whipple procedure (Table 1), for

---

Reprint requests: Dr. C. S. Grant, c/o Section of Publications, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55901.

Submitted for publication: January 15, 1979.

0003-4932/79/0700/0001 $00.75 © J. B. Lippincott Company

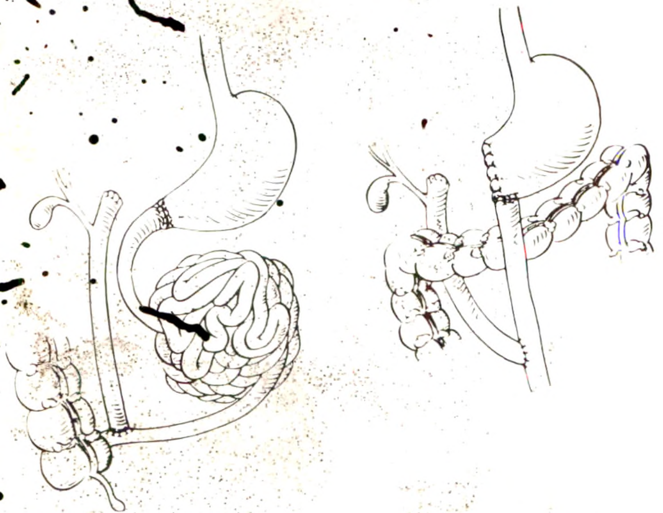


FIG. 1. Mann-Williamson preparation (left) and Roux-en-Y reconstruction (right) after gastric resection.

an overall ulcer incidence of 6%. The average interval from operation to diagnosis of ulcer was 1.25 years, with a range from one month to 12 years.

Findings and Comment

There is a definite risk of developing an anastomotic ulcer after either operation, and a gastric resection of 50% is inadequate to prevent ulceration. The symptoms, complications and virulence generally associated with anastomotic ulcers were the same in our series as in others (Table 2). Two-thirds of the patients had evidence of bleeding, and even more importantly, the death of the patient was at least partially caused by the ulcer in 22%.

Several pathophysiologic causes can be postulated to account for the ulcerogenic potential specifically related to these operations:

1) The long intestinal loop separating the pancreas and the bile duct from the gastric outlet could allow excessive absorption of the alkaline intestinal fluid; thereby less fluid would be available at the gastrojejunostomy to neutralize the gastric acid.

2) An inadequate gastric resection was done.

3) With postoperative pancreatic duct stenosis, often suspected to occur subtly and insidiously, the neutralizing capacity of the secretions is negated.

4) Gastric inhibitory polypeptide, an intestinal polypeptide only recently isolated and whose actions are not yet fully characterized, can inhibit gastric acid secretion (in response to histamine, pentagastrin and insulin hypoglycemia).[13] Recently, data have suggested an important axis between gastrin and gastric inhibitory polypeptide for the control of acid secretion.[14] Resection of the antrum, a major portion of the pancreas and the entire duodenum alters this hormone balance, perhaps resulting in an ulcerogenic situation.

5) Humoral, mucosal and other factors, as yet unknown, might be significant.

In an attempt to identify those patients at risk of developing anastomotic ulcers, patients having total pancreatectomy were compared with those having a Whipple operation (Fig. 3). The chance of developing an anastomotic ulcer was 6% for a patient surviving five years after a Whipple procedure and 18% for a patient surviving five years after total pancreatectomy. Thus, total pancreatectomy is statistically more ulcerogenic than radical pancreatoduodenectomy.

If the data are compared by disease categories, the risk of developing an ulcer, as it relates to those specific diseases, can be assessed (Fig. 4). The risk of ulcer after operation for pancreatitis is substantial. However, because the number of patients in each category is

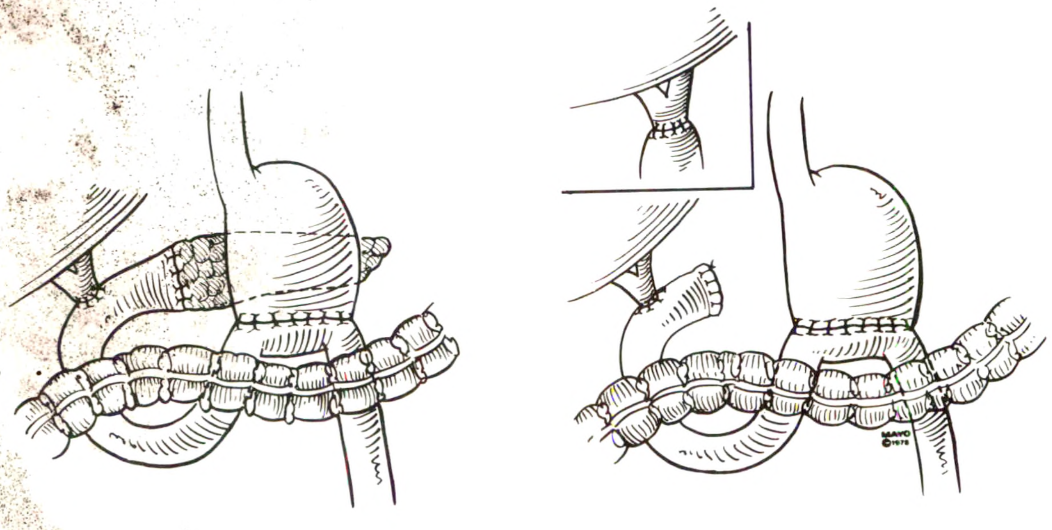


FIG. 2. Methods of reconstruction using Whipple procedure (left) and total pancreatectomy (right) for present series.

TABLE 1. *Pertinent Data on 18 Patients with Marginal Ulceration After Whipple Procedure or Total Pancreatectomy*

Case Number	Disease	Primary Operation	Per Cent Gastric Resection	Interval Between Operation and Diagnosis of Ulcer (mo)	Complications	Ulcer Treatment	Follow-up
1	Pancreatitis	Total pancreatectomy	40	3	Obstruction, pain	Bilateral vagotomy	3 yr, alive
2	Gr 2 Ca in head of pancreas	Whipple	67	144	Bleeding, pain	Medical	16 yr, alive
3	Gr 1 Ca of ampulla	Whipple	67	14	Pain	Medical	10 yr, dead
4	Gr 2 Ca in head of pancreas	Whipple	50	20	Pain	Bilateral vagotomy	2 yr, dead, Ca
5	Gr 2 Ca in head of pancreas	Whipple	50	20	Bleeding, pain	Bilateral vagotomy, resect. ulcer	3 yr, recurrent Ca
6	Pancreatitis	Total pancreatectomy	50	26	Bleeding, pain	Bilateral vagotomy	5 yr, alive
7	Pancreatitis	Total pancreatectomy	50	3	Bleeding	Medical	6 mo, dead*
8	Gr 2 Ca in head of pancreas	Whipple	50	2	Bleeding, pain	Surgical, no vagotomy	2 mo, dead*
9	Gr 2 Ca in distal common bile duct	Whipple	50	96	Bleeding	Medical	8 yr, dead
10	Pancreatitis	Whipple	60	36	Pain	Medical	8 yr, alive
11	Gr 3 Ca in head of pancreas	Whipple	40	5	Bleeding	—	Found at autopsy*
12	Gr 2 Ca in head of pancreas	Total pancreatectomy	50	2	Bleeding, pain	Medical	2 yr, dead, Ca
13	Gr 1 islet cell Ca	Total pancreatectomy	50	1	Pain	Medical	4 yr, dead, Ca
14	Gr 1 Ca of papilla	Whipple	67	36	Bleeding	Medical	3½ yr, dead
15	Gr 2 Ca of duodenum	Total pancreatectomy	40	1	Perforation, bleeding, pain	Oversew bilateral vagotomy	Died post-op*
16	Gr 2 Ca of ampulla	Whipple	50	15	Bleeding, pain	Advised vagotomy, refused	2 yr recurrent Ca
17	Pancreatitis	Whipple	40	72	Bleeding, pain	Medical	9 yr, alive
18	Pancreatitis	Total pancreatectomy	50	11	Pain	Medical	3 yr, alive

* Ulcer was major contributing factor to death.

relatively small, this risk is not statistically greater than the risk for the other disease groups.

In summary: 1) There is an increased risk of developing anastomotic ulcers after either subtotal or total pancreatectomy. 2) Anastomotic ulcers are severe complications. 3) Statistically, total pancreatectomy is more ulcerogenic than is radical pancreatoduodenectomy. 4) The basic cause of anastomotic ulceration in this setting is unknown.

The question is, "What means can be used to diminish the occurrence of ulcer?" Every effort should be made to keep the afferent loop short and to maintain the patency of the pancreatic duct. Perhaps the most imposing problem is whether higher gastric resection or vagectomy or both (or neither) should be employed. A high gastric resection accompanying total pancreatectomy can leave the patient a nutritional cripple. If the pancreatic duct becomes stenotic after a Whipple procedure, the patient would be just as disabled. Thus, a higher gastric resection does not seem to be a viable solution.

The use of vagectomy necessitates serious considera-

TABLE 2. *Incidence of Symptoms and Complications of Anastomotic Ulceration in Present Series and in Series Reported in the Literature*

Complication	Present Series* (18 pt)		Literature (%)
	No.	Per Cent	
Obstruction	1	6	5–19[11,16]
Bleeding	12	67	20–63[1,6]
Pain	14	77	43–95[2,12]
Free perforation	1	6	1–9[17,21]
Gastrojejunocolic fistula	0	0	1–5[3,21]

* Four deaths (22%).

tion as to the risks of the added operating time, immediate complications, and late postvagectomy syndromes. These patients already have experienced variable postoperative sequelae that may include insulin-dependent diabetes, dumping syndrome, steatorrhea, diarrhea, and weight loss. Therefore the risk of adding vagectomy cannot be dealt with lightly.

Finally, patient survival evaluated by disease category should be considered (Fig. 5). Patients with periampullary cancer have a dismal prognosis, whereas patients with pancreatitis have a near-normal survival.

On the basis of these data, the following conclusions are reasonable:

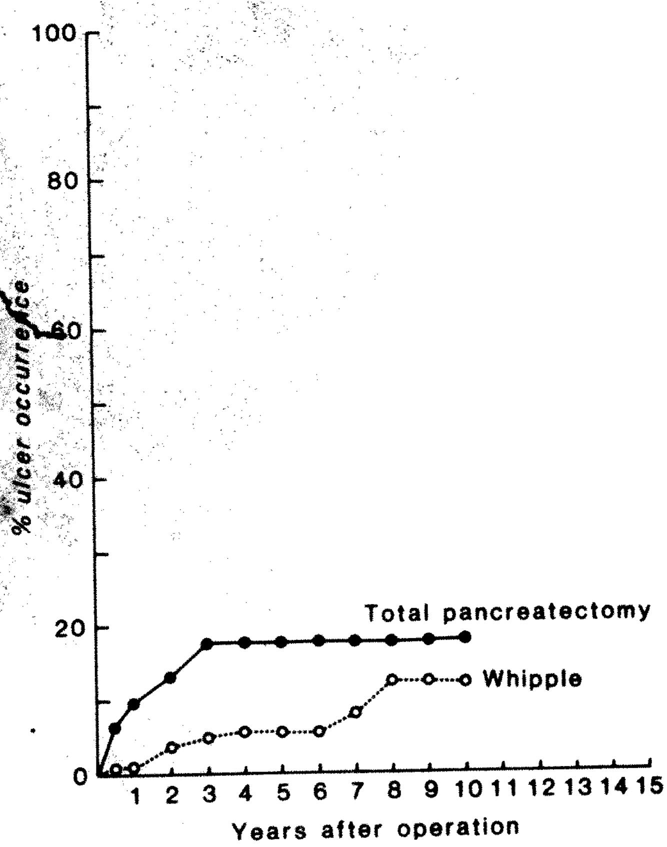


FIG. 3. Incidence of anastomotic ulcer comparing Whipple procedure with total pancreatectomy ($p < 0.05$).

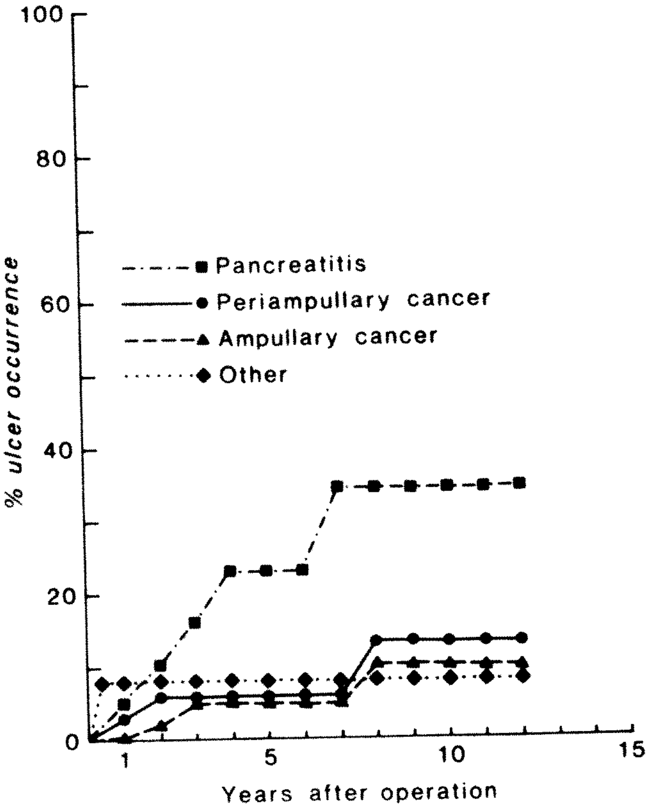


FIG. 4. Incidence of anastomotic ulcer in patients with different primary diseases.

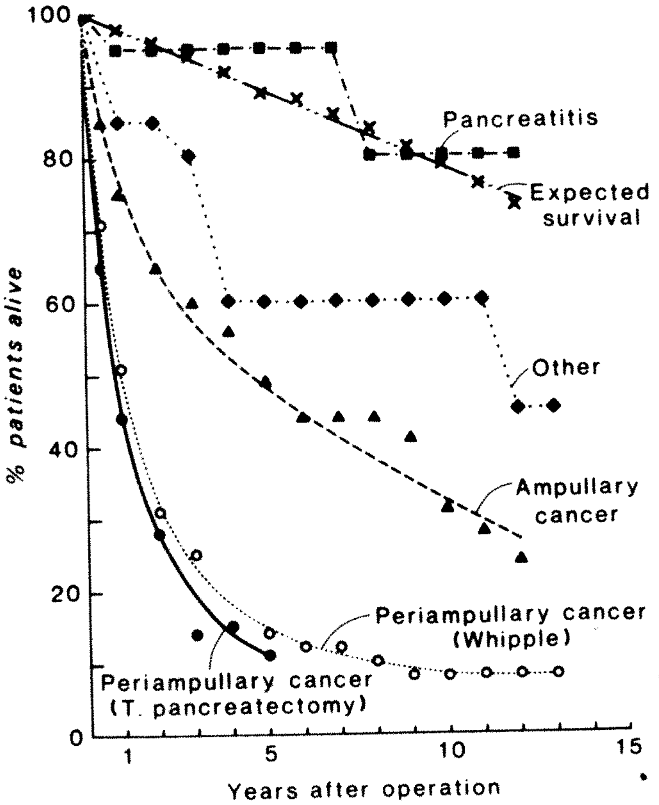


FIG. 5. Survival curves of patients having undergone radical surgery for different diseases.

1) For patients who undergo total pancreatectomy for benign disease, ampullary carcinoma resected for cure, or perhaps a low-grade periampullary carcinoma without nodal metastasis, the addition of vagectomy should be considered.

2) Although total pancreatectomy is statistically more ulcerogenic than the Whipple procedure, the risk of developing an ulcer after a Whipple procedure would eventually approach that after total pancreatectomy if follow-up is sufficiently long. Using this rationale, one could reasonably justify adding vagectomy to a Whipple procedure for patients with a favorable prognosis.

3) If a patient has a history of peptic ulceration, the incorporation of vagectomy would be strongly urged with either operation.

4) For patients with an anastomotic ulcer, regardless of the antecedent operation, aggressive surgical treatment with few exceptions remains the proper therapy.

References

1. Balint, J. A., Cooper, G. W., Price, E. C. V., et al.: The Management of Anastomotic Ulcer. Lancet, 2:551, 1957.
2. Cleator, I. G. M., Holubitsky, I. B. and Harrison, R. C.: Anastomotic Ulceration. Ann. Surg., 179:339, 1974.
3. Condon, J. R. and Tanner, N. C.: Retrospective Review of 208 Proved Cases of Anastomotic Ulcer. Gut, 9:438, 1968.
4. Du Plessis, D. J. and Mieny, C. J.: Stomal Ulceration Complicating the "Triple Anastomosis" Operation for Carcinoma of the Head of the Pancreas. S. Afr. J. Surg., 10:125, 1972.
5. Elliott, D. W.: Effect of Lost Pancreatic Juice on Gastric Acid and Peptic Ulcer. Am. J. Surg., 127:658, 1974.
6. Everson, T. C. and Allen, M. J.: Gastrojejunal Ulceration. Arch. Surg., 69:140, 1954.
7. Gobbel, W. G., Jr. and Shoulders, H. H., Jr.: Gastric resection. *In* Postlethwait, R. W. and Thoroughman, J. C. (eds.) Results of Surgery for Peptic Ulcer (A Cooperative Study by Twelve Veterans Administration Hospitals). Philadelphia, W. B. Saunders Company, 1963, p. 142.
8. Goligher, J. C., De Dombal, F. T., Duthie, H. L., et al.: Five- to Eight-year Results of Leeds/York Controlled Trial of Elective Surgery for Duodenal Ulcer. Br. Med. J., 2:781, 1968.
9. Herrington, J. L., Jr., Edwards, W. H. and Edwards, L. W.: Re-evaluation of the Surgical Treatment of Duodenal Ulcer. Surgery, 49:540, 1961.
10. Howard, R. J., Murphy, W. R. and Humphrey, E. W.: A Prospective Randomized Study of the Elective Surgical Treatment for Duodenal Ulcer: Two- to Ten-Year Follow-up Study. Surgery, 73:256, 1973.
11. Jaffe, B. M., Newton, W. T., Judd, D. R., et al.: Surgical Management of Recurrent Peptic Ulcers. Am. J. Surg., 117: 214, 1969.
12. Nuboer, J. F.: Recurrent Ulceration After Surgical Treatment of Gastro-duodenal Peptic Ulcer. Ann. R. Coll. Surg. Engl., 28:303, 1961.
13. Pederson, R. A. and Brown, J. C.: Inhibition of Histamine-, Pentagastrin-, and Insulin-Stimulated Canine Gastric Secretion by Pure "Gastric Inhibitory Polypeptide." Gastroenterology, 62:393, 1972.
14. Sirinek, K. R., Cataland, S., O'Dorisio, T. M., et al.: Augmented Gastric Inhibitory Polypeptide Response to Intraduodenal Glucose by Exogenous Gastrin and Cholecystokinin. Surgery, 82:438, 1977.
15. Stabile, B. E. and Passaro, E., Jr.: Recurrent Peptic Ulcer. Gastroenterology, 70:124, 1976.
16. Stuart, M. and Hoerr, S. O.: Recurrent Peptic Ulcer Following Primary Operations with Vagotomy for Duodenal Ulcer. Arch. Surg., 103:129, 1971.
17. Thompson, J. E. and Dailey, T. H.: Recurrent Ulceration After Operation for Peptic Ulcer: Results After Gastroenterostomy, Gastrectomy and Vagotomy in 64 Cases. Ann. Surg., 163: 704, 1966.
18. Waddell, W. R. and Loughry, R. W.: Gastric Acid Secretion After Pancreaticoduodenectomy. Arch. Surg., 96:574, 1968.
19. Walters, W. and ReMine, W. H.: Appraisal of the Various Operations for Peptic Ulcer. Surgery, 55:585, 1964.
20. Warren, K. W., Poulantzas, J. K. and Kune, G. A.: Life After Total Pancreatectomy for Chronic Pancreatitis: Clinical Study of Eight Cases. Ann Surg., 164:830, 1966.
21. Wychulis, A. R., Priestley, J. T. and Foulk, W. T.: A Study of 360 Patients With Gastrojejunal Ulceration. Surg. Gynecol. Obstet., 122:89, 1966.

Sensitivity of the Canine Pancreatic Intraductal Pressure to Subclinical Reduction in Cholinesterase Activity

T. D. DRESSEL, M.D., R. L. GOODALE, JR., M.D., D. B. HUNNINGHAKE, M.D.,* J. W. BORNER

As a continuation of work from this laboratory on anticholinesterase induced pancreatitis, a study of the relationship between reduced serum cholinesterase activity and changes in pancreatic intraductal pressure was undertaken. Pharmakokinetic studies in three dogs revealed rapid reduction in serum cholinesterase activity following an IV bolus dose of the cholinesterase inhibitor 0,0-diethyl-0-(2-isopropyl-6-methyl-4-pyrimidinyl)phosphorothioate. Following each dose of cholinesterase inhibitor, stable levels of cholinesterase inhibition were reached in 30 minutes. In four dogs the pancreatic duct was perfused from the tail of the ventral pancreas and intraductal pressures measured. A total of 25 mg/kg of the cholinesterase inhibitor was given in 5 mg/kg doses 30 minutes apart, and serum cholinesterase measured 30 minutes after each dose. Mean pressures were established over a 15 minute interval. Linear regression analysis of 23 data points revealed a significant ($p < 0.001$) cumulative dose-related increase in pancreatic intraductal pressure [Pressure (cm saline) = 14.2 + 1.03 × Cumulative Dose (mg/kg)] and significant ($p < 0.001$) negative correlation between serum cholinesterase activity and intraductal pressure [Pressure (cm saline) = 48.0 − 0.057 × Esterase Activity (mU/ml)]. These data suggest that, in dogs, reduced cholinesterase activity is directly related to increased pancreatic intraductal pressure, and it may be a factor in the pathogenesis of pancreatitis.

From the Departments of General Surgery and Pharmacology of the University of Minnesota, Minneapolis, Minnesota

INCREASED PANCREATIC INTRADUCTAL pressure is commonly considered an etiologic factor in acute pancreatitis. Anatomic studies have demonstrated the presence of smooth muscle in the feline pancreatic duct,[7] canine pancreatiduodenal junction[5] and the human pancreatic sphincter.[3] Extensive sympathetic and parasympathetic innervation to the papilla of Vater, ampullary region of the duodenum and head of the pancreas have been demonstrated in man and dog.[23] Increased autonomic nervous system activity could theoretically result in increased smooth muscle tone and increased pancreatic intraductal pressure. Considerable controversy exists, however, regarding the effect of the autonomic nervous system on ampullary tone. Anrep[1] noted that peripheral vagal stimulation in the dog caused an increase in the volume of the pancreas associated with stimulation of pancreatic secretion. These findings were consistent with ductal or sphincter contraction with resultant intrapancreatic retention of secretions. Studies by Koravitsky[13] and Lenninger[15,16] extended these findings and demonstrated that in cats, pilocarpine, methacholine and vagal stimulation caused simultaneous stimulation of pancreatic secretions and increased ductal resistance. Using the technique of direct measurement of canine pancreatic intraductal pressure, Menguy[18] noted transient (less than ten minutes) and minimal (1.2–6.4 cm H_2O) pressure increase following intravenous pilocarpine in pharmacologic doses. He concluded that the response to pilocarpine was one of increased fluctuation, *i.e.*, increased peristaltic tone in duodenum and ducts, rather than a prolonged pressure increase. Tansy[22] reported that both peripheral vagal stimulation and ductal infusions of bethanechol produced slight pressure elevations in dogs, but he concluded that the ductal orifice probably behaves as a passive flutter valve. Finally, Gilsdorf[8] had demonstrated, in dogs, increased pancreatic intraductal pressure during sympathetic nervous system stimulation and decreased pressure during parasympathetic stimulation. In an attempt to resolve this controversy, it is the purpose of this study to investigate the effects of a potent, irreversible cholinesterase inhibitor on pancreatic intraductal pressure.

We previously reported that pancreatitis and a pseudocyst occurred in a patient following intoxication by an anticholinesterase insecticide.[4] The irreversible

---

* Department of Pharmacology.

Reprint requests: T. D. Dressel, M.D., University of Minnesota, Box 230 Mayo Building, 420 Delaware Street, S.E., Minneapolis, Minnesota 55455.

Supported by the Ralph and Marian Falk Surgical Research Foundation and EPA Grant R806561-01-0.

Submitted for publication: December 22, 1978.

0003-4932/79/0700/0006 $00.85 © J. B. Lippincott Company

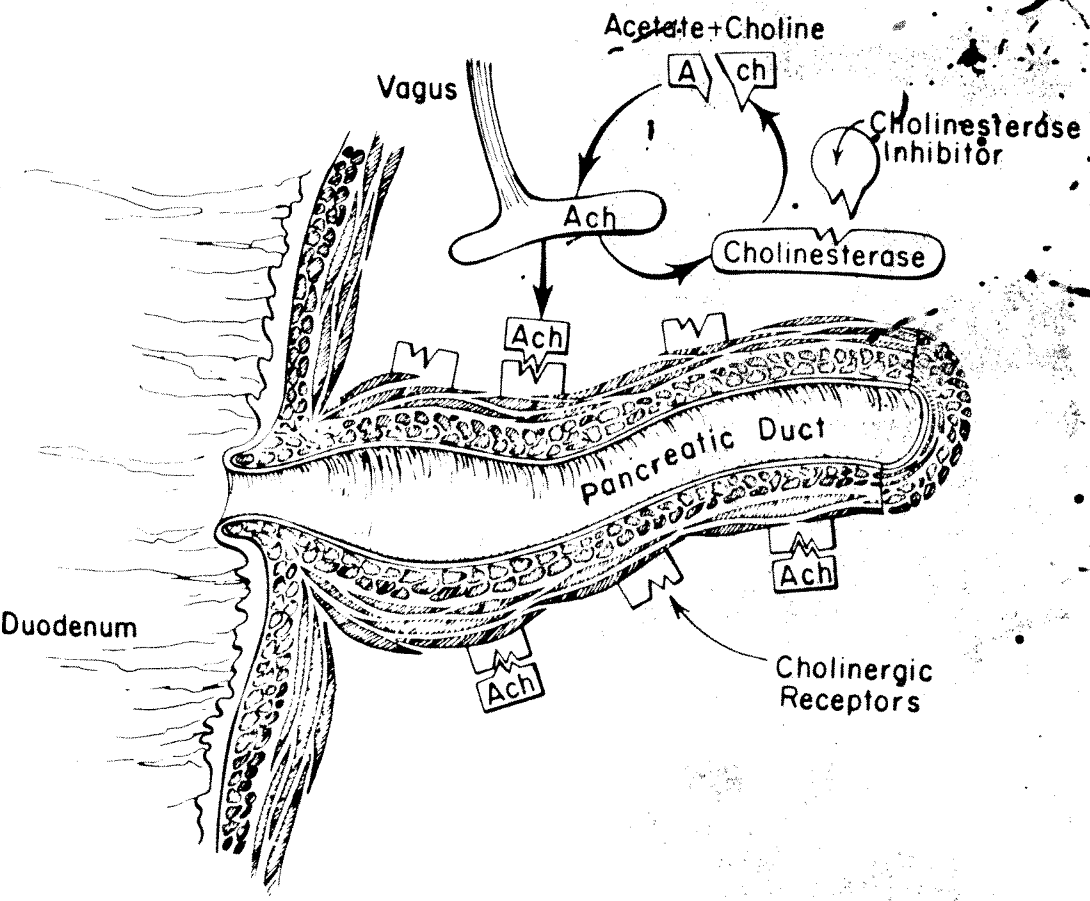


FIG. 1. Artist's concept of the canine pancreatic duodenal junction (major ampulla). Post ganglionic vagal fibers release acetylcholine (Ach) and cause the contraction of the smooth muscle. Acetylcholine is hydrolized by cholinesterase and acetylcholinesterase to acetate (A) and choline (Ch). Inhibition of cholinesterase or acetylcholinesterase results in a larger number of cholinergic receptors occupied and increased smooth muscle tone.

organophosphate type anticholinesterases are commonly used as insecticides, and over 220 million pounds are manufactured annually in the United States.[24] Anticholinesterase intoxication causes depression of cholinesterase activity and accumulation of acetylcholine at postsynaptic receptors, and it results in profound sustained stimulation of skeletal muscle, central nervous system and the autonomic nervous system. Clinically, intoxication with the lipid soluble cholinesterase inhibitors results in a preponderance of parasympathetic symptoms, including bradycardia, salivation, lacrimation and diarrhea.[9] Figure 1 shows the relationships between acetylcholine, cholinesterase and cholinesterase inhibitors at the pancreatoduodenal junction.

Methods

Three mongrel dogs (15–18 kg) were anesthetized with pentobarbital sodium, 30 mg/kg. A single dose of the anticholinesterase 0.0-diethyl-0-(2-isopropyl-6-methyl-4-pyrimidinyl)phosphorothioate,† was given through a foreleg vein at time = zero. One dog received anticholinesterase, 5 mg/kg, another dog received 15 mg/kg, and the third received 25 mg/kg. Prior to administering anticholinesterase and at 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 minutes, venous blood was collected via an indwelling femoral venous catheter. The specimens were immediately centrifuged, and the serum stored at 4°. These storage conditions have been shown to result in stable serum cholinesterase levels for at least 37 days.[14] Within 30 days, serum cholinesterase activity was determined by the method of Ellman.[6] The results of the experiment are shown in Figure 2. There is a rapid reduction of the serum cholinesterase activity after a single dose of the anticholinesterase. Within 30 minutes, the serum cholinesterase activity has been reduced to essentially its equilibrium level. Therefore a 30 minutes sampling interval was chosen for the following experiment.

Four mongrel dogs, 16–20 kg, were anesthetized with pentobarbital, 30 mg/kg; and through a laparotomy, the tail of the ventral pancreas was transected. The duct was cannulated with a polyethylene catheter ID = 0.584 mm, OD = 0.905 mm. The catheter was

---

† Diazinon, Ciba Geigy Corporation.

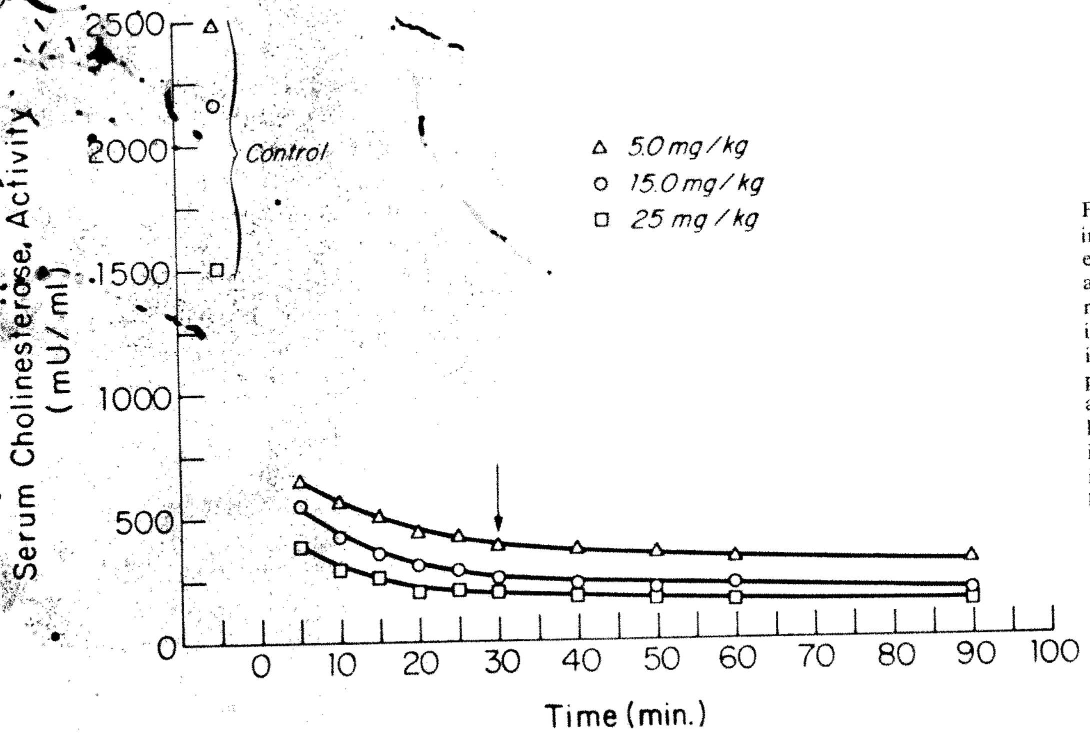


FIG. 2. Time course of inhibition of serum cholinesterase activity following a single dose of the irreversible cholinesterase inhibitor 0,0-diethyl-0(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate. At each of three dosage levels there is a rapid inhibition of enzyme activity reaching plateau levels by 30 minutes (arrow).

advanced to 3 cm from the ampulla and secured in place with a ligature. The pancreatic duct was perfused with normal saline at 37° through the catheter at constant flow of 0.76 cc/min by means of a Harvard pump. The pressure at the catheter tip was visually monitored by a saline monometer and continuously recorded by a Stathem pressure transducer and Sanborn recorder (Fig. 3). After a 30 minute control period, the dogs received a series of IV injections of the anticholinesterase 0,0-diethyl-0-(2-isopropyl-6-methyl-4-pyrimidinyl)phosphorothioate. A total dose of 25 mg/kg was given in 5.0 mg/kg increments, each 30 minutes apart. Thirty minutes after the last dose of cholinesterase inhibitor, atropine, 75 μg/kg, was given IV. Pancreatic intraductal pressure was tabulated every five minutes. In the calculation of the time averaged pressure response, the first 15 minutes followed each dose of anticholinesterase was deleted to allow for equilibration. Immediately prior to each dose of cholinesterase inhibitor, venous blood was obtained for determination

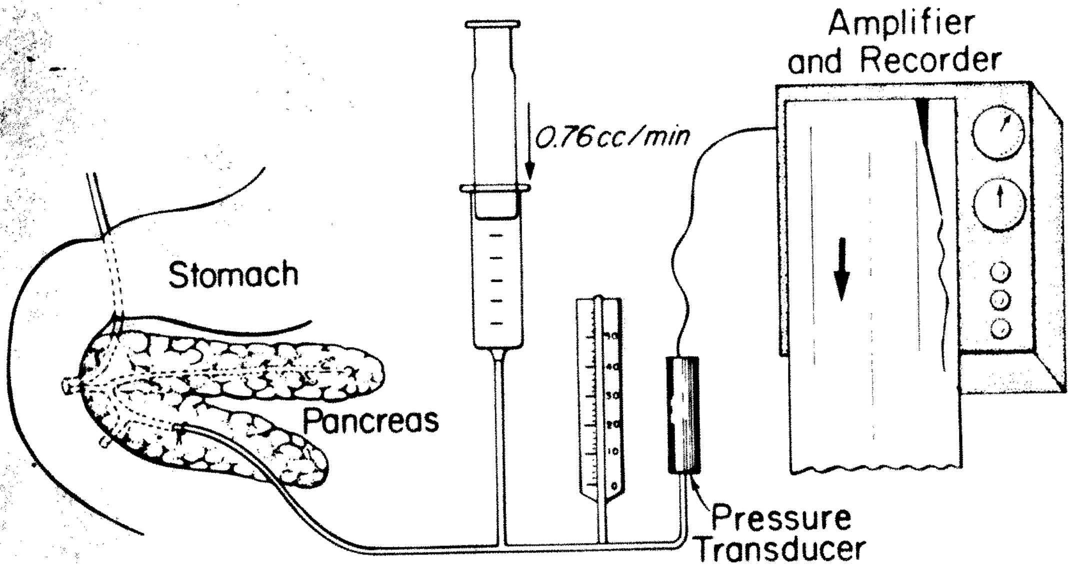


FIG. 3. Schematic drawing of apparatus for measuring and recording pancreatic intraductal pressure.

of serum cholinesterase activity. The peripheral pulse rate was determined at 30 minute intervals throughout the experiment by palpation of femoral artery pulse for 30 seconds count, and the dogs were observed for signs of excessive cholinergic activity, *i.e.*, salivation, lacrimation, diarrhea, muscle fasciculations.

Results

Figure 4 shows the response of the pancreatic intraductal pressure to a series of 5 mg/kg doses of anticholinesterase in dog #577. There is an increase in mean pancreatic intraductal pressure following four of five doses of the anticholinesterase. Atropine 75 μg/kg resulted in an immediate reduction in pancreatic intraductal pressure. Four dogs provided 23 data points (catheter malfunction in dog #400 eliminated one data point at 25 mg/kg). Following 20 of the 23 doses of anticholinesterase, there was an increase in mean pancreatic intraductal pressure (Fig. 5). Linear regression analysis, using a least square fit to the mean pressure levels, reveals a significant correlation between the cumulative dose of cholinesterase inhibitor and pancreatic intraductal pressure: Pressure (cm saline) = 14.2 + 1.03 × Dose (mg/kg), $R = 0.86$, $p < 0.001$. Atropine, 75 μg/kg IV, completely reversed the pressure changes of the cholinesterase inhibitor and returned the pressure to control levels (Fig. 5).

The control serum cholinesterase levels were 2150, 984, 1662, and 1415 mU/ml in dogs #577, #339, #482, and #400 respectively and were not in any way correlated with control pancreatic intraductal pressure (see discussion). However, after the first dose and for each subsequent dose of cholinesterase inhibitor, there was a significant negative correlation between the remaining serum cholinesterase activity and pancreatic intraductal pressure: Pressure (cm saline) = 48.0 − 0.057 × Esterase Activity (mU/ml), $R = -.81$, $p < 0.001$ (Fig. 6).

The pulse rate did not significantly change throughout the experiment and was not correlated with either the cumulative dose of cholinesterase inhibitor or level of cholinesterase activity. The control pulse rate was 152 ± 5.9 (mean ± SEM). Following a total of 25 mg/kg of Diazinon, the pulse rate was 149 ± 4.8 ($p > 0.6$). Mild muscle fasciculations occurred in all dogs at a total dose of 25 mg/kg; but salivation, lacrimation or diarrhea was not observed.

Discussion

Enzymes catalyzing the hydrolysis of choline esters have been shown to play an important role in the regula-

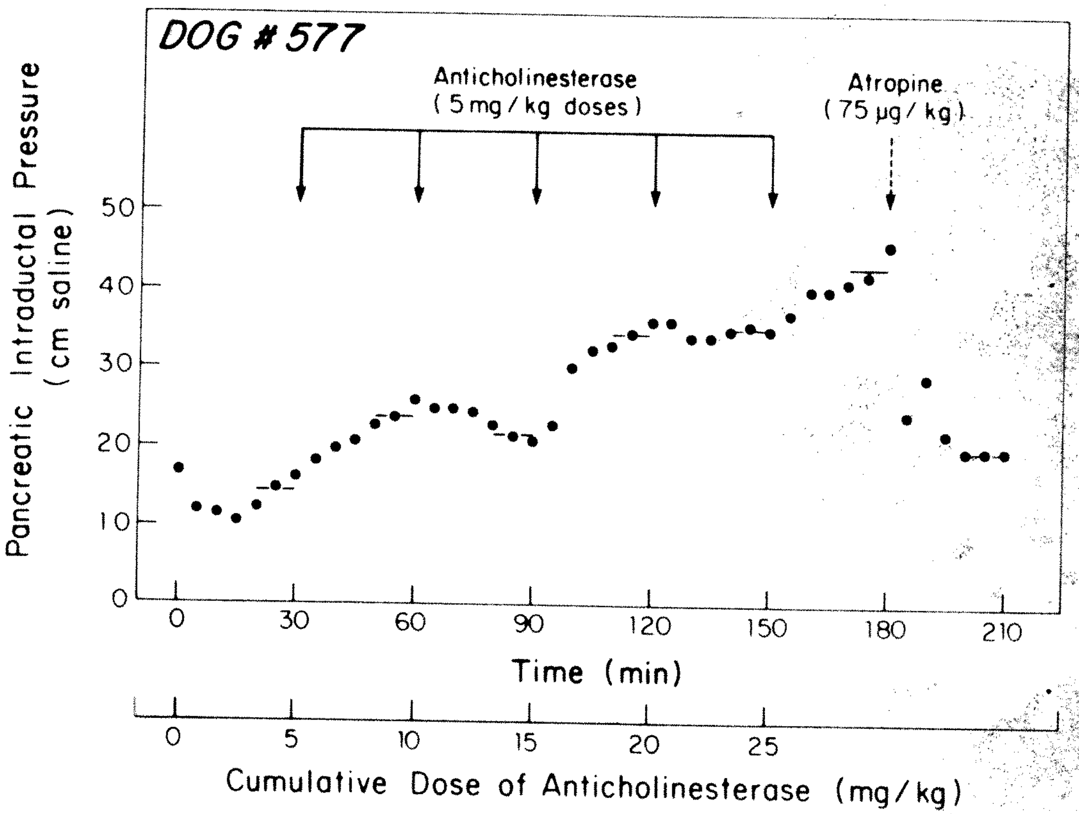


FIG. 4. The time course of pancreatic intraductal pressure is shown for dog #577. A series of 5 mg/kg doses of cholinesterase inhibitor results in an increase in intraductal pressure. Mean pressures were determined over a 15 minute interval prior to each dose of inhibitor (horizontal lines) and were used to establish linear regression line shown in Figures 5 and 6.

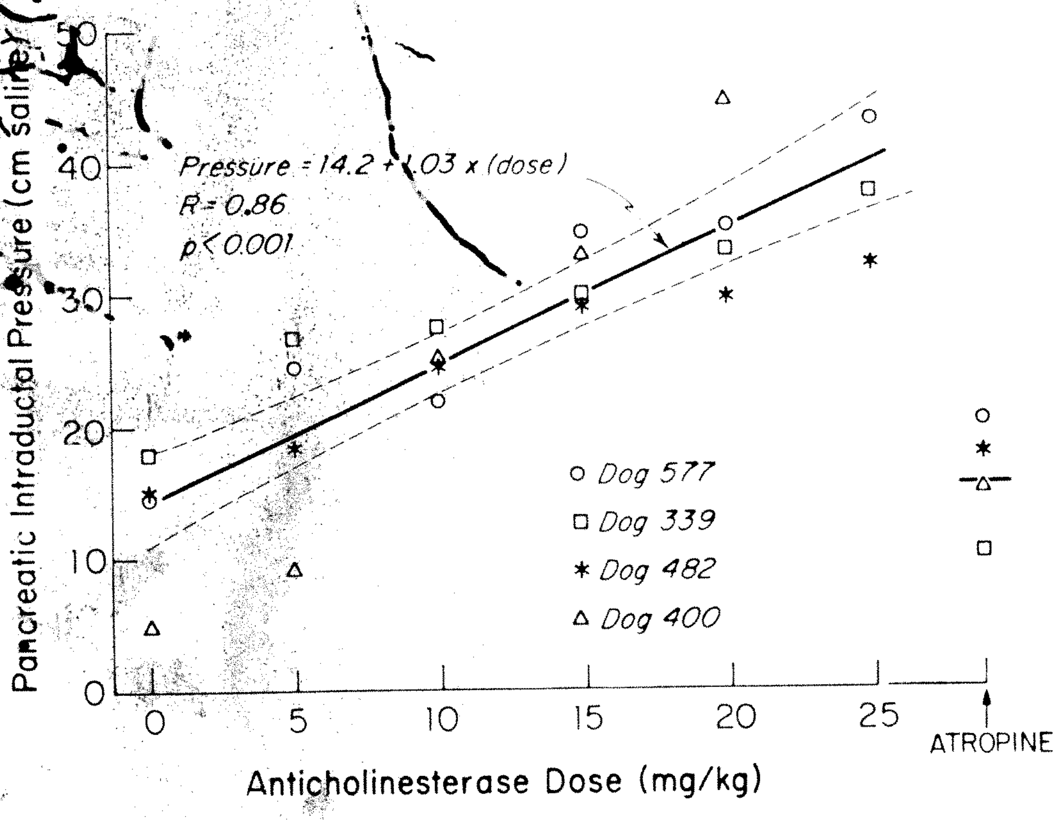


FIG. 5. Anticholinesterase given in 5 mg/kg doses 30 minutes apart, caused a dose dependent increase in pancreatic intraductal pressure. This pressure rise is completely blocked by atropine 75 μg/kg. The regression line is established by a least square analysis of the data points. The dotted lines indicate the 95% confidence limits of the regression line.

tion of neuromuscular activity.[2,20] The cholinesterase activity of whole blood has been resolved into two types, a particulate or membrane bound species associated with the erythrocyte membrane, and a soluble form present in the serum or plasma. Studies of the differential specificities of these two enzymes have led to their designation as acetylcholinesterase and cholinesterase (or pseudocholinesterase) respectively.[2] The study of the rate of enzyme inhibition revealed a rapid inhibition of serum cholinesterase activity following intravenous administration of Diazinon. Equilibrium levels of activity are reached within 30 minutes. These findings are in general agreement with the results of other investigators.[25]

The results of this study clearly demonstrate that a dose related increase in pancreatic intraductal pressure follows IV administration of a potent cholinesterase inhibitor. Other investigators noted only mild and transient elevations in pancreatic intraductal pressure, following cholinergic stimulation;[18] but this study reveals prolonged high pressures. Tachyphylaxis is not observed in this study, and pressure levels are reached which can result in interstitial extravasation of pancreatic fluid.[11] These pressure elevations occur at low doses of cholinesterase inhibitor that have no significant effect on the heart rate of the dogs, and produce only mild muscle fasciculations without neuromuscular blockade. This may be the result of an exquisite sensitivity of the canine pancreatic sphincter to tonic cholinergic stimulation. Smooth muscle is intrinsically slow to react to stimuli, and the minimal pressure elevations observed by other investigators may be due to the short duration of action of intravenous bolus parasympathomimetic agents. Depletion of acetylcholine at synaptic junctions may explain the transient response to electrical vagal stimulation. The biological effect of a cholinesterase inhibitor is determined by its distribution within the organism, its ability to penetrate tissue barriers, and its affinity for various tissues.[17] The inhibitor used in this experiment may have a selective high affinity for the cholinesterase of the ampullary or ductal smooth muscle. Finally, pancreatic juice contains cholinesterase activity[10] which increases following parasympathomimetic stimuli (unpublished data from this Laboratory). Thus, cholinesterase may act within the duct or ampulla to modulate smooth muscle tone during cholinergic stimulation. This may represent a mechanism for feedback inhibition of cholinergic stimuli on ductal smooth muscle. The administration of an anticholinesterase could conceivably inhibit the intraductal cholinesterase, block this feedback inhibition, and result in the sustained high pressure observed in this experiment.

The initial control serum cholinesterase activity is

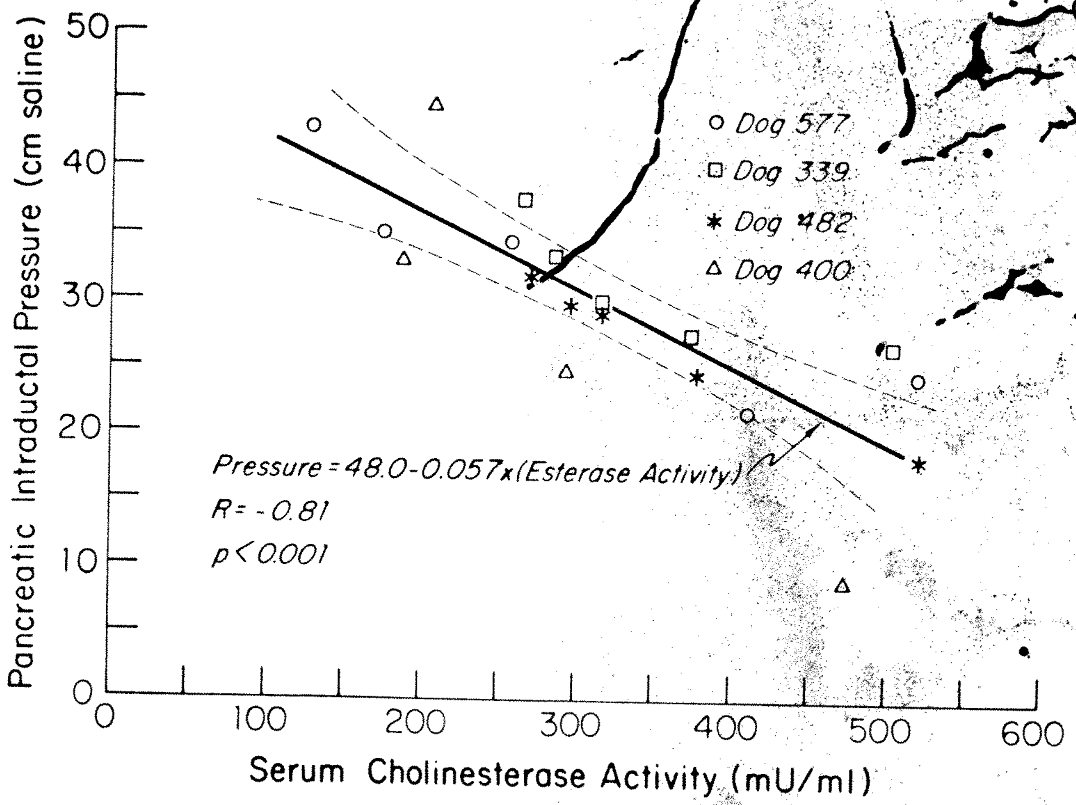


FIG. 6. Serum cholinesterase was determined 30 minutes following each dose of anticholinesterase. The intraductal pressure is negatively correlated with the cholinesterase activity remaining. The dotted lines indicate the 95% confidence limits of the least square regression line.

not correlated with the control intraductal pressure. This may be due to individual variations in control basal vagal tone or to variations in basal endogenous cholecystokinin level, a factor which is well known to affect ampullary tone.[21] The first dose of anticholinesterase invariably results in at least 50% inhibition of serum activity (range 51–75%). At greater degrees of inhibition, linear regression analysis of the data reveals a significant negative correlation between the remaining cholinesterase activity and intraductal pressure. These data suggest that in the range of cholinesterase activity from 100 to 500 mU/ml, cholinesterase acts in some way to maintain ductal patency. These results are in general agreement with those of Koelle[12] and Riker[19] who observed no effects of cholinesterase inhibition until 50–80% of the enzymatic activity has been destroyed. Cholinesterase is apparently present in a two to five fold excess of that required for regulation of neuromuscular activity.

The cholinesterase inhibitor in these canine experiments is capable of producing a sustained functional pancreatic ductal obstruction (at subclinical dosage levels) that is completely reversible by atropine. It is unknown whether this capability is unique to the cholinesterase inhibitor used in this study or is common to all drugs or toxins that may reduce cholinesterase activity through direct inhibition or reduced synthesis of the enzyme. It is also unknown to what extent subclinical acute and chronic exposure to these compounds contributes to pancreatic disease in man.

References

1. Anrep, G. V.: The Influence of the Vagus on Pancreatic Secretion. J. Physiol., 50:421, 1915.
2. Augustinsson, K.: Cholinesterase. A Study on Comparative Enzymology. Acta Physiol. Scand., 15, Sup. 52, 1948.
3. Bergh, G. S.: The Sphincter Mechanism of the Common Bile Duct in Human Subjects. Surgery, 11:299, 1942.
4. Dressel, T. D., Goodale, R. L., Arneson, M. A and Borner, J. W.: Pancreatitis as a Complication of Anticholinesterase Insecticide Intoxication. Ann. Surg., 189:199, 1979.
5. Eichhorn, E. P. and Boyden, E. A.: The choledochoduodenal junction in the dog—A restudy of Oddi's sphincter. Am. J. Anat., 97:431, 1955.
6. Ellman, G. L., Courtney, D., Andres, V. and Featherstone, R. M.: A New and Rapid Colorimetric Determination of Acetylcholinesterase Activity. Biochem. Pharmacol., 7:88, 1961.
7. Garrett, J. R., Alm, P. and Lenninger, S.: Smooth Muscle of the Pancreatic Duct of the Cat and its Innervation. Experientia, 29:842, 1973.
8. Gilsdorf, R. G., Urdaneta, L. F., Delaney, J. P. and Leonard, A. S.: Central Nervous System Influences on Pancreatic Secretion, Sphincteric Mechanisms and Blood Flow and Their Role in the Course of Pancreatitis. Surgery, 62(4):581, 1967.
9. Goodman, L. and Gilman, A.: The Pharmacological Basis of Therapeutics. Fourth Edition. New York, MacMillan Co., 1970, p. 450.
10. Hebb, C. and Hill, K.: Distribution of Cholinesterase in the Mammalian Pancreas. Q. J. Exp. Physiol., 40:168, 1955A.

11. Herring, P. T. and Simpson, S.: The Pressure of Pancreatic Secretion, and the mode of Absorption of Pancreatic Juice After Obstruction of the Main Ducts of the Pancreas. Q. J. Exp. Physiol. 2:99, 1909.
12. Koelle, G. and Gilman, A.: The Relationship Between Cholinesterase Inhibition and the Pharmacological Action of Di-Isopropyl Fluorophosphate (DFP). J. Pharm. Exp. Therap., 87:421, 1946.
13. Korovitsky, L. K.: The Part Played by the Ducts in the Pancreatic Secretion. J. Physiol., 57:215, 1923.
14. [illegible]nks, K. W. and Sklar, G. S.: Stability of Pseudocholinesterase in Stored Blood. Anesthesiology, 44(5):428, 1976.
15. Lenninger, S.: Effects of Parasympathomimetic Agents and Vagal Stimulation on the Flow in the Pancreatic Duct of the Cat. Acta Physiol. Scand., 82:345, 1971.
16. Lenninger, S. and Olin, T.: The Effect of Methacholine on the Pancreatic Duct of the Cat Studied with a Radiological Method. Scand. J. Gastroenterol., 7:727, 1972.
17. Loshadkin, N. A. and Smirnov, V. V.: A Review of Modern Literature on the Chemistry and Toxicology or Organophosphorus Inhibitors of Cholinesterases. Associated Technical Service, Inc., 1962. Knunyants, I. L. and Markov, S. M. (eds.) p. 74.
18. Menguy, R. B., Hallenbeck, G. A., Bollman, J. L. and Grindlay, J. H.: Intraductal Pressure and Sphincteric Resistance in Canine Pancreatic and Biliary Ducts After Various Stimuli. Surg. Gynecol. Obstet., 106:306, 1958.
19. Riker, W. and Weseoc, W.: The Relationship Between Cholinesterase Inhibition and Function in a Neuroeffector System. J. Pharm. Exp. Therap., 95:515, 1949.
20. Rosenberry, T. L.: Acetylcholinesterase. Advan. in Enzymol., 43:103, 1975.
21. Sandblom, P., Voegtlin, W. L. and Ivy, A. C.: The Effect of Cholecystokinin on the Choledochoduodenal Mechanism (Sphincter of Oddi). Am. J. Physiol., 113:175, 1935.
22. Tansy, M. F., Salkin, L. M., Innes, D. L., et al.: The Occlusive Competence of the Duodenal Orifice of the Canine Pancreatic Duct. Surg. Gynecol. Obstet., 144:856, 1977.
23. Tiscornia, O. M., Martinez, J. L. and Sarles, H.: Some Aspects of Human and Canine Macroscopic Pancreas Innervation. Am. J. Gastroenterol., 66:353, 1976.
24. United States International Trade Commission. Synthetic Organic Chemicals. United States Production and Sales, 1976. USITC Publication #833.
25. Vandekar, M. and Heath, D. F.: The Reactivation of Cholinesterase After Inhibition in Vivo by Some Dimethyl Phosphate Esters. Biochem. J., 67:202, 1957.

Protease Inhibitors and Experimental Acute Hemorrhagic Pancreatitis

TADAO MANABE, M.D., MICHAEL L. STEER, M.D.*

Proteolytic enzyme inhibitors have been reported to decrease morbidity and mortality from certain types of experimental pancreatitis, although recent randomized trials have been unable to demonstrate that they are of benefit in the treatment of clinical acute pancreatitis. We have evaluated the effect of two proteolytic enzyme inhibitors (trasylol and chlorophyll-a) on experimental acute pancreatitis induced in mice by the feeding of a choline-deficient ethionine-enriched diet. The mortality rate and the biochemical and morphological severity of pancreatitis were not altered by either trasylol or chlorophyll-a administration. Thus, in this respect, diet-induced pancreatitis appears to resemble clinical acute pancreatitis. The reasons for the lack of effectiveness of proteolytic enzyme inhibitors in the treatment of both forms of pancreatitis are discussed.

From the Department of Surgery, Beth Israel Hospital and Harvard Medical School, 330 Brookline Avenue, Boston, Massachusetts

THE MOST SEVERE FORMS of acute pancreatitis are characterized by hemorrhage and necrosis of the pancreas which is generally believed to reflect damage that results from the intrapancreatic activation of digestive enzymes such as trypsinogen. This belief has led to the suggestion that acute pancreatitis might be effectively treated by the administration of proteolytic enzyme inhibitors.[1,5,21] Indeed, proteolytic enzyme inhibitors such as trasylol (aprotonin) and chlorophyll-a have been shown to reduce the mortality rate of experimental pancreatitis.[10,13,15,16,18,22] In contrast, however, recent randomized trials have failed to show that administration of proteolytic enzyme inhibitors alters the course of clinical acute pancreatitis.[8,14]

In this communication, we report that proteolytic enzyme inhibitors do not alter the course of the acute hemorrhagic necrotizing pancreatitis which follows administration of a choline-deficient ethionine-enriched (CDE) diet to young female mice. CDE diet-induced acute pancreatitis has many features which make it an attractive model for the study of pancreatitis. The observed lack of response to protease inhibitors may indicate that this model of acute pancreatitis more closely resembles the clinical disease than do other models, and may help elucidate the reasons that protease inhibitors are ineffective in the treatment of clinical acute pancreatitis.

Materials and Methods

Female CD-1 mice, weighing 12–15 g, obtained from Charles River Laboratories, were used in all experiments. Trasylol was purchased from Sigma and chlorophyll-a was provided by Dr. Sadao Saito, Nampo Pharmaceutical Co., Tokyo, Japan. Sincalide (the synthetic C-terminal octapeptide of CCK-PZ) was a gift from E. R. Squibb, Ltd., Princeton, N.J. Pancreatitis was induced by feeding mice a choline-deficient ethionine-enriched (CDE) diet (2 g/mouse/day) prepared according to the method of Lombardi et al.[9]

Effects of Protease Inhibitors on CDE Diet-Induced Pancreatitis

The effects of trasylol and chlorophyll-a were examined in separate experiments. In each case, mice were initially fasted for 30 hours and then given the CDE diet for 24 hours. Mice were randomly assigned to three study groups as follows: no treatment, "low dose" protease inhibitor, and "high dose" protease inhibitor. For the trasylol studies, "low dose" treatment consisted of intraperitoneal injections of trasylol (10 units/g body weight) every eight hours for 48 hours beginning with the commencement of CDE diet administration (*i.e.*, six injections), while the "high dose" group received 100 units/g body weight injections of trasylol at the same times. In the chlorophyll-a studies,

---

* Recipient of Research Career Development Award #NS00160 from the National Institute of Neurological and Communicative Disorders and Stroke.

Reprint requests: Michael L. Steer, M.D., Beth Israel Hospital, 330 Brookline Avenue, Boston, Massachusetts 02215.

Supported by grant #AM20302 from the National Institute of Arthritis, Metabolism and Digestive Diseases.

Submitted for publication: December 18, 1978.

0003-4932/79/0700/0013 $00.75 © J. B. Lippincott Company

"low dose" treatment consisted of a single intraperitoneal injection of chlorophyll-a (2 μg/g body weight) at the time of CDE diet commencement (*i.e.*, one injection). The "high dose" chlorophyll-a group received 2 μg/g body weight of chlorophyll-a intraperitoneally at the time of CDE diet commencement as well as 12 and 24 hours later (*i.e.*, three injections). After 24 hours of CDE diet administration all animals were fasted for 24 hours, and then 9–18 animals in each group were killed. The pancreas was rapidly removed and processed for microscopic examination and *in vitro* secretory studies (see below). The remaining mice in each group were given regular laboratory chow and observed for an additional four days to determine mortality rates.

Effects of Protease Inhibitors on Normal Mice

After a 30 hour fast, mice were randomly assigned to various groups and given regular chow for 24 hours. Control mice received no protease inhibitors while the trasylol group received intraperitoneal injections of trasylol (100 units/g body weight) at eight hour intervals over the 48 hour beginning with resumption of feeding (*i.e.*, six injections). The chlorophyll-a group received intraperitoneal injections of chlorophyll-a (2 μg/g body weight) at 12 hour intervals over the 24 hours beginning with resumption of feeding (*i.e.*, three injections). After 24 hours of feeding, all animals were fasted for 24 hours and then sacrificed by decapitation. The pancreas was processed for *in vitro* secretory studies (see below).

In Vitro *Effects of Protease Inhibitors*

After an 18 hour fast, normal mice were killed. The pancreas was removed and processed for *in vitro* secretory studies which were performed in the presence of trasylol or chlorophyll-a.

Microscopic Studies

Fragments of pancreas were fixed in 10% formalin and embedded in paraffin. Sections were stained with hematoxalin-eosin and examined by light microscopy.

In Vitro *Secretory Studies*

The pancreas was placed in Krebs-Henseleit bicarbonate buffer containing 5.6 mM glucose and gassed with 95% O_2 and 5% CO_2 mixture at 37°. The pancreata were cut into five to six fragments which were pooled, washed in buffer and reallocated to incubation vessels containing 3 ml of buffer such that each vessel contained the fragments equivalent to one to one and a half pancreata. The vessels were gassed with 95% O_2 and 5% CO_2, tightly covered, and preincubated at 37° for 30 minutes while being continuously shaken (100/min). Following this period of preincubation, the buffer was removed and replaced with fresh medium containing test substances, gassed, covered, and incubated for an additional 30 minutes at 37° while shaking. Sincalide (the C-terminal octapeptide of CCK-PZ) was present at a concentration (0.3 ng/ml) previously demonstrated to produce submaximal rates of protein and enzyme secretion. After incubation, the pancreatic fragments were removed, blotted, weighed, and homogenized in 6 ml of phosphate buffer (2×10^{-2} M, pH 6.9 containing 4×10^{-3} M NaCl). The incubation media and homogenate samples were centrifuged to clarity (7000 × g, 10 min), and their supernatants assayed for protein and digestive enzymes. Protein was measured using the method of Lowry et al.[11] with bovine serum albumin as the standard. Amylase was assayed according to the method of Bernfeld[2] with soluble starch as the substrate. One unit of activity is defined as that which liberates 1 mg equivalent of maltose in three minutes at 30°. Trypsinogen was measured as trypsin after activation with enterokinase for three hours at 30°, and chymotrypsinogen was measured as chymotrypsin after activation with bovine trypsin for two hours at 4°.[6] Trypsin was assayed using TAME as the substrate, and chymotrypsin assayed using BTEE as the substrate according to the method of Hummel.[7]

Analysis of Data

The statistical significance of changes noted was evaluated using Student's t-test and x^2 analysis.[3] Statistically significant differences were defined as those with a p value of <.05.

Results

Protease Inhibitors and CDE Diet-induced Pancreatitis

Administration of the CDE diet for one day was associated with a 57% four day mortality rate in untreated mice (Table 1). Neither "low dose" nor "high dose" trasylol administration significantly altered the observed mortality rate. Similarly, neither "low dose" nor "high dose" chlorophyll-a altered the mortality rate of pancreatitis (Table 1).

The pancreatic content of amylase as well as the *in vitro* rate of protein and amylase secretion were markedly increased during CDE diet-induced pancreatitis (compare "0" dose groups in Table 3 with "0" dose group in Table 2). Neither trasylol nor chlorophyll-a, in either dose, significantly altered these characteristic features of diet-induced pancreatitis (Table 2).

TABLE 1. *Effect of Protease Inhibitors on Mortality from Diet-induced Pancreatitis*

			Day 1		Day 2		Day 3		Day 4	
Agent	n	Dose	Mortality	Per Cent	Mortality	Per Cent	Mortality	Per Cent	Mortality	Per Cent
Trasylol	28	0	0/28	0	8/28	29	11/28	39	16/28	57
	27	low	0/27	0	6/27	22	11/27	41	17/27	63
	27	high	0/27	0	11/27	41	[illegible]/27	48	19/27	70
Chlorophyll-a	40	0	0/40	0	8/40	20	16/40	40	23/40	57
	40	low	0/40	0	9/40	22	17/40	42	25/40	[illegible]
	40	high	0/40	0	7/40	17	15/40	38	23/40	57

The CDE diet was given for one day. "n" refers to the number of animals in each group. No statistically significant differences in mortality rates among the groups was noted (χ^2 analysis, $p > .05$). Further details are given in the text.

CDE diet-induced pancreatitis is microscopically characterized by widespread areas of edema, congestion, and necrosis. Normal acinar basophilia is lost and the cells are filled with zymogen granules and clear cytoplasmic vacuoles.[9] Neither trasylol nor chlorophyll-a, at either dose, altered the severity of pancreatitis noted microscopically.

Protease Inhibitors and the Normal Pancreas

Administration of trasylol or chlorophyll-a to mice not exposed to the CDE diet did not result in significant changes in pancreatic digestive enzyme content or *in vitro* secretion (Table 3). Trasylol, but not chlorophyll-a, when added to the *in vitro* incubation media reduced the level of trypsin and chymotrypsin activity after zymogen activation (Table 4). Although this might suggest that zymogen output had been reduced, this may be more apparent than real since significant levels of trasylol were also carried over into the assay mixture after zymogen activation and could, therefore, have led to a lowering of measured enzyme activity without actually altering zymogen secretion. A similar response to chlorophyll-a would not be expected since chlorophyll, in the form of chlorophyll-a, is not an effective protease inhibitor (see below).

Discussion

Young female mice given a choline-deficient ethionine-enriched diet develop acute hemorrhagic pancreatic necrosis and uniformly die after four days of diet administration.[10] The pancreatic lesion closely resembles clinical acute pancreatitis both morphologically and biochemically.[19] This model has many features which make it suitable for studies directed at evaluating the efficacy of various therapies for acute pancreatitis. Because mice are inexpensive and easily handled, studies utilizing large numbers of animals can be performed and the statistical significance of effects can be defined. The severity of pancreatitis can be adjusted by varying the amount of CDE diet administered as well as the duration of exposure to the diet. For example, when mice are given the diet for only one day, the mortality rate is reduced from the 100% noted with four day exposure to the diet to only 50–60% (Table 1). The greatest value of this model, however, results from the observation that pancreatitis does not develop immediately but, rather evolves over a period of several days. This allows the investigator to induce pancreatitis *in vivo* and subsequently to study the behavior of the diseased gland *in vitro*. We have previously reported that CDE diet-induced pancreatitis

TABLE 2. In Vitro *Secretion During Diet-induced Pancreatitis*

Agent	n	Dose	Amylase Content (U/g tissue)	Amylase Output U/g tissue/30′	Protein Output mg/g tissue/30′
Trasylol	6	0	29,012 ± 1338	4243 ± 460	10.3 ± 0.8
	6	low	25,154 ± 851	4522 ± 530	9.3 ± 1.1
	6	high	29,598 ± 776	4242 ± 282	10.2 ± 0.8
Chlorophyll-a	12	0	27,682 ± 889	4290 ± 232	14.3 ± 0.5
	12	low	26,828 ± 1619	4110 ± 330	15.0 ± 1.1
	9	high	26,556 ± 321	4732 ± 79	16.2 ± 0.7

Trasylol or chlorophyll-a were given by intraperitoneal injection, and secretion studied *in vitro* in the presence of Sincalide. Results represent mean ± SEM, and "n" denotes number of animals in each group studied. No statistically significant differences between 0, low and high dose groups were noted (t-test, $p > .05$). Further details are given in the text.

TABLE 3. *Effect of Protease Inhibitors on the Normal Mouse Pancreas*

Agent	n	Dose	Amylase Content (U/g)	Amylase Output (U/g/30′)	Protein Output (mg/g)	Trypsinogen Content (U/g)	Trypsinogen Output (U/g/30′)	Chymotrypsinogen Content (U/g)	Chymotrypsinogen Output (U/g/30′)
Trasylol	9	0	8938 ± 314	1157 ± 124	5.4 ± 0.2	130.2 ± 15.8	38.2 ± 2.9	182.0 ± 4.9	23.9 ± 1.1
	9	high	9018 ± 6[illegible]3	1145 ± 123	5.4 ± 0.3	152.3 ± 18.4	40.0 ± 2.6	210.6 ± 15.1	29.5 ± 2.3
Chlorophyll-a	6	0	10687 ± 440	1458 ± 85	4.6 ± 0.1	138.3 ± 3.1	51.6 ± 0.8	151.7 ± 6.2	32.6 ± 1.6
	6	high	12114 ± 445	1796 ± 173	5.1 ± 0.5	138.3 ± 3.4	56.5 ± 2.3	160.9 ± 7.5	34.9 ± 3.1

Protease inhibitors were given by intraperitoneal injection, and pancreatic secretion studied *in vitro* in the presence of Sincalide. Results represent mean ± SEM and "n" denotes number of animals in each group. No statistically significant differences between the 0 and high dose groups were noted (t-test, $p > .05$). Further details are given in the text.

is characterized by an elevated pancreatic content of digestive enzymes and an accelerated rate of *in vitro* enzyme secretion. The magnitude of these changes closely parallel the severity of pancreatitis noted microscopically as well as the mortality rate observed.[12]

In this communication, we have evaluated the effects of proteolytic enzyme inhibitors on diet-induced pancreatitis. The CDE diet was given for only one day as it was hoped that this more mild form of pancreatitis would respond to the administration of protease inhibitors. Two types of proteolytic enzyme inhibitors were studied. Trasylol, which is a low molecular weight protein, complexes with proteolytic enzymes and results in their inactivation. Chlorophyll-a, on the other hand, is not an active enzyme inhibitor. It is believed to be converted, *in vivo*, to chlorophyllin which is a potent inhibitor of trypsin and other proteases.[17] Both trasylol and chlorophyll-a have been reported to improve survival from experimental pancreatitis,[13,15,16,18,22] and in some studies, to beneficially alter the course of clinical pancreatitis.[20]

Our studies fail to show that either of the protease inhibitors alters the mortality rate of CDE diet-induced pancreatitis. In addition, the microscopic severity of CDE diet-induced pancreatitis was not altered by either of these agents. It should be noted that trasylol and chlorophyll-a were given in doses equal to or higher than those previously reported to be effective in both clinical and experimental pancreatitis. We chose to administer the protease inhibitors by intraperitoneal injection as intravenous infusion is impractical in mice, and intraperitoneal administration of these agents has been previously reported to be effective in experimental pancreatitis.[4,18] In addition, our studies show that, when given to normal mice, these doses of the protease inhibitors do not induce pancreatic abnormalities (Table 3).

The observed failure of protease inhibitors to alter the course of CDE diet-induced pancreatitis is not surprising in view of recent *randomized* clinical trials of trasylol which show that this agent does not alter the course of clinical pancreatitis.[8,14] The reason(s) that protease inhibitors are effective in the treatment of some forms of experimental pancreatitis (*i.e.*, those induced by intraductal or interparenchymal injection of irritating agents) but fail to alter the course of CDE diet-induced and clinical pancreatitis have not been elucidated, but an understanding of these observations would be of considerable clinical and theoretical import. One might speculate that experimental pancreatitis induced by ductal or parenchymal injection is triggered by the rapid liberation of activated proteolytic enzymes

TABLE 4. *Effects of* In Vitro *Addition of Protease Inhibitors on the Normal Mouse Pancreas*

Agent	Concentration	n	Amylase Content (U/g)	Amylase Output (U/g/30′)	Protein Output (mg/g)	Trypsinogen* Content (U/g)	Trypsinogen* Output (U/g/30′)	Chymotrypsinogen† Content (U/g)	Chymotrypsinogen† Output (U/g/30′)
Trasylol	0	6	9214 ± 152	2054 ± 58	6.4 ± 0.2	168.0 ± 11.7	49.4 ± 4.1	159.0 ± 11.1	34.7 ± 3.3
	60 U/ml	6	9147 ± 340	2112 ± 85	6.3 ± 0.2	160.0 ± 17.3	5.8 ± 2.0**	147.6 ± 16.4	23.9 ± 2.7*
	600 U/ml	6	9555 ± 231	1974 ± 148	7.2 ± 0.3	137.5 ± 8.7	8.7 ± 0.9**	130.1 ± 8.2	0.2 ± 0.2**
Chlorophyll-a	0	6	9399 ± 592	1671 ± 20	6.1 ± 0.2	166.1 ± 3.9	48.4 ± 5.6	168.0 ± 6.2	32.2 ± 2.8
	(1×10^{-4} M)	6	8901 ± 549	1521 ± 92	6.0 ± 0.3	141.5 ± 10.8	41.3 ± 2.0	145.7 ± 6.3	25.6 ± 0.7

Protease inhibitors were added to the *in vitro* incubation media, and secretion studied in the presence of Sincalide. Results represent mean ± SEM, and "n" denotes number of animals in each group. Statistical significance of differences between groups given protease inhibitor and those given no protease inhibitor was evaluated using t-test. *indicates $p < .05$, and **indicates $p < .001$.

† Zymogen content and output were measured by assay of proteolytic activity after zymogen activation.

within the gland parenchyma and/or ductal system (*i.e.*, areas of the pancreas which may be accessible to exogenously administered protease inhibitors). In contrast, clinical and CDE diet-induced pancreatitis may initially involve intracellular activation of proteolytic enzymes. At this stage, these enzymes would not be accessible to exogenously administered inhibitors and would, therefore, remain capable of inducing cell necrosis. Once necrosis develops, concomitant microvascular changes probably prevent exogenously administered protease inhibitors from reaching areas of the gland containing the activated enzymes. As a result, administration of proteolytic enzyme inhibitors would not alter the course of either clinical acute pancreatitis or CDE diet-induced pancreatitis.

References

1. Bedacht, R.: Treatment of pancreatitis with a Kallikrein Inactivator. Arzneim. Forsch., 12:371, 1958.
2. Bernfeld, P.: α and β. Methods Enzymol., 1:149, 1955.
3. Colton, T.: Statistics in Medicine. Boston, Little, Brown and Company, 1974.
4. Dembinska-Kiec, A.: The Influence of Aprotinin (Trasylol) on Experimental Acute Necrosis of the Pancreas in Rats. Acta Med. Pol., 13:1, 1972.
5. Frey, E. K., Kraut, H. and Werle, E.: Kallikrein (Glumorin). Stuttgart, Ferd. Enke. 1950.
6. Glazer, G. and Steer, M. L.: Requirements for Activation of Trypsinogen and Chymotrypsinogen in Rabbit Pancreatic Juice. Anal. Biochem., 77:130, 1977.
7. Hummel, B. C. W.: A Modified Spectrophotometric Determination of Chymotrypsin, Trypsin and Thrombin. Can. J. Biochem. Physiol., 37:1393, 1959.
8. Imrie, C. W., Benjamin, I. S., Ferguson, J. C., et al.: A Single-centre Double-blind Trial of Trasylol Therapy in Primary Acute Pancreatitis. Br. J. Surg., 65:337, 1978.
9. Lombardi, B., Estes, L. W. and Longnecker, D. S.: Acute Hemorrhagic Pancreatitis (Massive Necrosis) with Fat Necrosis Induced in Mice by DL-ethionine Fed with a Choline-deficient Diet. Am. J. Pathol., 79:[illegible]65, 197[illegible]
10. Lombardi, B. and Rao, N. K.: Acute Hemorrhagic Pancreatic Necrosis in Mice. Influence of Age and Sex of the Animals and Dietary Ethionine, Choline, Methionine, and Adenine Sulfate. Am. J. Pathol., 81:87, 1975.
11. Lowry, O. H., Rosebrough, N. J., Farr, A. L. and Randall, R. J.: Protein Measurement with the Folin Phenol Reagent. J. Biol. Chem., 193:265, 1951.
12. Manabe, T. and Steer, M. L.: Experimental Acute Pancreatitis in Mice: Protective Effects of Glucagon. Gastroente[illegible] 76:529, 1979.
13. McCutcheon, A. D. and Race, D.: Experimental Pancreatitis: Use of a New Antiproteolytic Substance, Trasylol. Ann. Surg., 158:233, 1963.
14. M.R.C. Working Party: Death From Acute Pancreatitis. M.R.C. Multicentre Trial of Glucagon and Aprotinin. Lancet, 632, 1977.
15. Nemir, P., Jr., Hoferichter, J. and Drabkin, D. L.: The Protective Effect of Proteinase Inhibitor in Acute Necrotizing Pancreatitis: An Experimental Study. Ann. Surg., 158:655, 1963.
16. Nugent, F. W., Henderson, M. E., Jonasson, H., et al.: The Effect of a Kallikrein-trypsin Inactivator in Experimental Pancreatitis. Lahey Clin. Bull., 13:167, 1964.
17. Oda, T., Yokono, O., Yoshida, A., et al: On the Successful Treatment of Pancreatitis with Chlorophyll-a and Inhibitory Effects of its Derivatives on Trypsin and Other Protease Activities in Vitro. Gastroenterol. Jap., 6:49, 1971.
18. Orda, R., Wiznitzer, T., Bawnik, J. B. and Bubis, J. J.: Effect of Chlorophyll-a in Experimental Acute Pancreatitis. Intraperitoneal Treatment in the Guinea Pig. Chir. Gastroenterol. (Gastroent. Surg.), 9:269, 1975.
19. Rao, N. K. and Lombardi, B.: Acute Hemorrhagic Pancreatic Necrosis in Mice. Intraparenchymal Activation of Zymogens, and Other Enzyme Changes in Pancreas and Serum. Gastroenterology, 70:720, 1976.
20. Trapnell, J. E., Rigby, C. C., Talbot, C. H. and Duncan, E. H. L.: A Controlled Trial of Trasylol in the Treatment of Acute Pancreatitis. Br. J. Surg., 61:177, 1974.
21. Werle, E., Tauber, K., Hartenback, W. and Forell, M. M.: Treatment of Acute Pancreatitis. Muench. Med. Wochenschr., 100:1265, 1958.
22. Wiznitzer, T., Orda, R., Bawnik, J. B. and Bubis, J. J.: Acute Necrotizing Pancreatitis in the Guinea Pig. Effect of Chlorophyll-a on Survival Times. Am. J. Dig. Dis., 21:459, 1976.

Infusion of the Branched Chain Amino Acids in Postoperative Patients

Anticatabolic Properties

HERBERT FREUND, M.D., HERBERT C. HOOVER, JR., M.D., SUSAN ATAMIAN, R.N., JOSEF E. FISCHER, M.D.

Postinjury metabolism is characterized by breakdown of muscle protein as substrate for energy production and gluconeogenesis and by the resultant loss of lean body mass and weight loss. The branched chain amino acids (BCAAs) which are principally oxidized by the skeletal muscle have been implicated in recent *in vitro* and *in vivo* studies as having special anticatabolic and regulating effects in skeletal muscle. We studied the anticatabolic effects of the BCAAs in 35 patients undergoing operative injury of moderate severity. In a prospective randomized and blinded manner patients were infused for five days starting immediately after surgery with either 5% dextrose or 5% dextrose with an amino acid solution containing 22, 35 or 100% BCAAs. All patients survived and there were no major postoperative complications. Mean hospital stay was 17 days for patients receiving amino acids and 19 days for patients receiving 5% dextrose only (p = ns). All three groups receiving amino acid solutions were in nitrogen equilibrium or in a slight positive nitrogen balance, while the group receiving 5% dextrose only was in a mean negative nitrogen balance of 6.6 ± 0.6 gN/day. The differences between the three groups receiving amino acids were slight and not significant. Weight loss was 2 ± 0.7 kg in the 5% dextrose group, 1 ± 0.7 kg in the 22% BCAAs group, 0.5 ± 0.5 kg in the 35% BCAAs group and the 100% BCAAs group gained 0.4 ± 1.8 kg. Blood chemistries in the different groups and during the study period remained within normal limits except for ammonia levels rising significantly in the 5% dextrose group and SGOT levels rising in the 22% and 35% BCAA groups. With mild variations the plasma amino acid patterns in all groups were similar to the normal pattern, even in the 100% BCAAs group receiving an unbalanced amino acid solution, suggesting the complete cessation of amino acid efflux from muscle, the muscle depending solely on the exogenous supply of BCAAs to satisfy its metabolic requirements. The results suggest that early nutritional suppport in the postoperative period will result in nitrogen equilibrium and that the infusion of the three BCAAs only in the postoperative state is as effective in preventing muscle catabolism as other more balanced amino acid solutions. In the postinjury state balanced amino acid solutions rich in BCAA may prove beneficial.

From the Department of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

POSTINJURY OR POSTOPERATIVE catabolism is associated with negative nitrogen balance, muscle protein breakdown and weight loss. Depending on the severity of the injury body protein is catabolized at a rate of 75–150 g/day, resulting in a loss of up to 300–600 g of lean body mass per day.

Recent studies have attributed special anticatabolic effects to the branched chain amino acids (BCAAs): valine leucine and isoleucine.[2,7,14] *In vitro* experiments have demonstrated that the BCAAs serve as energy substrate for the muscle, participate in gluconeogenesis through alanine and glutamine synthesis and play a crucial role in regulation of muscle protein degradation and synthesis.[2,7,13,14] *In vivo* studies in rats have confirmed and extended the *in vitro* studies by demonstrating that the nitrogen conserving quality of protein solutions in the postoperative period might be improved by modifying the composition of the solution infused in favor of BCAAs.[6] Moreover, the infusion of the three BCAAs alone resulted in nitrogen equilibrium and a relatively normal plasma and muscle amino acid pattern with the exception of raised branched chain amino acid and alanine. Walser, et al.[16–18] demonstrated prolonged improvement in nitrogen conservation by the administration of α-keto analogues of the BCAAs during fasting.

This study was undertaken to elucidate the role of the BCAAs in preventing or minimizing postinjury lean body mass breakdown, by the administration of solutions enriched in branched chain amino acids to patients immediately following operations of moderate severity.

The influence of the BCAAs on postoperative catabolism was studied in 35 patients undergoing operative injury of moderate degree. The results suggest that:

Reprint requests: Josef E. Fischer, M.D., Professor and Chairman, Department of Surgery, University of Cincinnati Medical Center, 231 Bethesda Avenue, Cincinnati, Ohio 45267.

Submitted for publication: January 15, 1979.

0003-4932/79/0700/0018 $00.80 © J. B. Lippincott Company

1) Early nutritional support can maintain nitrogen equilibrium in the early postoperative state.
2) Branched chain amino acids may play a central role in preventing postoperative catabolism.
3) Increasing the quantity of branched chain amino acids infused during the postinjury state or the percentage of branched chain amino acids in a given infusion mixture may result in improved nitrogen retention in the posttraumatic state.

Materials and Methods

Thirty-five adult patients with no prior history of weight loss and judged to be of normal nutritional status undergoing elective operative injury of moderate degree (Table 1) were studied in a prospectively randomized and blinded manner. Patients were assigned to one of four groups and starting immediately postoperative were infused for a total of five days with one of the following four solutions (Table 2):

I. 5% Dextrose—no amino acids (10 patients).
II. 3% Freamine® (containing 22% BCAAs) in 5% Dextrose (9 patients).
III. 3% FO80 (specially designed amino acid formulation, previously reported to be beneficial in the treatment of hepatic encephalopathy and containing 35% BCAAs)[5] in 5% Dextrose (9 patients).
IV. 3% protein solution containing only the three BCAAs in equimolar quantities (100% BCAA) in 5% Dextrose (7 patients).

All patients received 2000–3000 ml/24 hours of the designated solution and were kept NPO during the five days of the study.

TABLE 1. *Operative Procedures in 35 Patients*

Procedure	Number of Patients
Cholecystectomy	10
Cholecystectomy and choledochotomy	6
Exploratory laparotomy and adhesiolysis	5
Colectomy	6
Hiatus hernia repair	3
Colostomy closure	2
Gastrectomy-subtotal	3

Intake, output and body weight were recorded daily. Urine was collected daily and analyzed for total nitrogen as determined by the Kjeldahl method. Blood was drawn for amino acid analysis, urea, electrolytes, glucose, liver function tests, ammonia, hemoglobin, hematocrit and WBC, preoperatively and every other day.

All results are given as mean ± SEM and statistical significance determined by Student's t-test.

These studies were approved by the human studies committee of the Massachusetts General Hospital and informed consent was obtained from each patient.

Results

There were 17 males and 18 females among the group studied, their ages ranging from 21–75 years (mean 48.4 ± 3.0 years).

Patient population in all four groups were similar in respect to age, sex, nutritional status, diagnosis and type of operation.

TABLE 2. *Composition of the Various Solutions Used in This Study (g/100 ml)*

	5% Dextrose	Freamine II 3% in D5W (BCAA 22%)	F080 3% in D5W (BCAA 35%)	3% BCAA in D5W (100% BCAA)
Essentials:				
L—Isoleucine	—	0.208	0.337	1.000
L—Leucine	—	0.272	0.412	1.000
L—Valine	—	0.198	0.315	1.000
L—Lysine	—	0.219	0.228	—
DL—Methionine	—	0.159	0.037	—
L—Phelylalanine	—	0.169	0.037	—
L—Threonine	—	0.120	0.169	—
L—Tryptophan	—	0.046	0.028	—
Nonessentials:				
L—Alanine	—	0.212	0.281	—
L—Arginine	—	0.109	0.225	—
L—Histidine	—	0.085	0.090	—
L—Proline	—	0.335	0.300	—
L—Serine	—	0.176	0.187	—
—Glycine	—	0.600	0.337	—
L—Cysteine—HCl—H_2O	—	0.007	0.007	—
Total amino acids:	—	30.0 g/liter	30.0 g/liter	30.0 g/liter
Total nitrogen:	—	4.4 g/liter	4.5 g/liter	3.3 g/liter
Glucose:	50.0 g/liter	50.0 g/liter	50.0 g/liter	50.0 g/liter

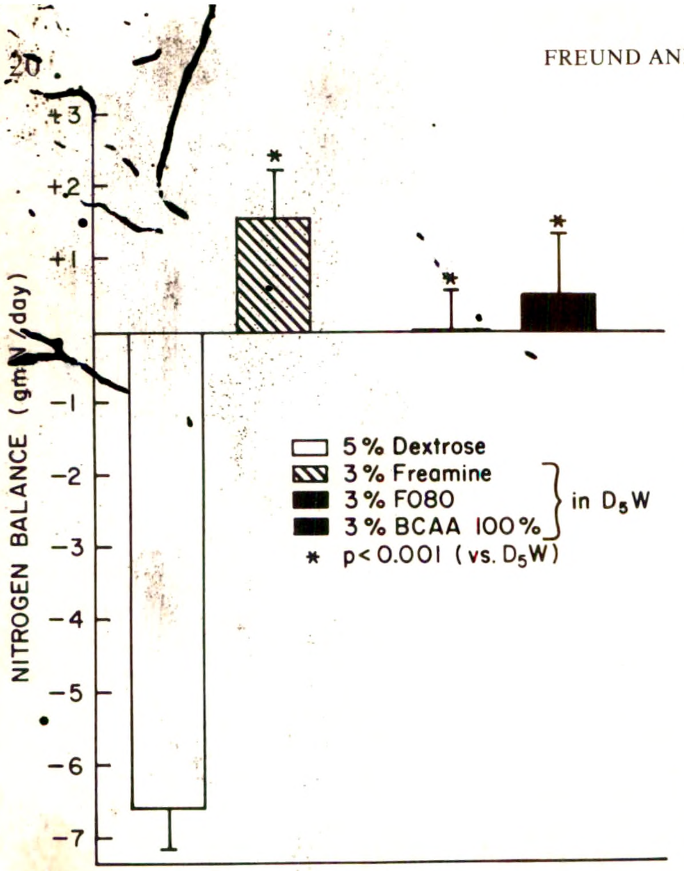


FIG. 1. Mean cumulative five day nitrogen balances in four groups of patients (n = 35) undergoing operative injury of moderate degree and infused postoperatively for five days with either 5% dextrose only or with 5% dextrose and one of three 3% amino acid formulations differing in their branched chain amino acid concentrations (mean ± SEM).

Clinical Course

All 35 patients included in this study survived surgery and left the hospital after a mean of 17 days for the Freamine (17.3 ± 1.4), FO80 (17.6 ± 2.3) and 100% BCAA (17.7 ± 3.1) groups and after a mean of 19.5 ± 2.9 days for the group receiving 5% dextrose only (p = ns). There were no major postoperative complications. One patient in each of the FO80 and 100% BCAA groups developed a urinary tract infection which cleared with antibiotic treatment.

Nitrogen Balance

The mean cumulative five day nitrogen balances in the four study groups are summarized in Figure 1, while the day to day nitrogen balances are documented in Table 3. All three groups of patients receiving amino acid solutions were in nitrogen equilibrium or in slight positive nitrogen balance. In comparison, in the group of patients receiving 5% dextrose only nitrogen balance was negative, at −6.6 ± 0.6 g N/day, this pattern holding true for the cumulative nitrogen balance as well as for each day separately ($p < 0.001$). The differences between the three groups receiving amino acids were only slight and not significant.

Body Weight (BW)

During the five day period of the study the patients infused with 5% dextrose only lost a mean 2.0 ± 0.7 kg of their BW, patients receiving 22% BCAA lost 1.0 ± 0.7 kg of their BW, patients receiving 35% BCAA lost 0.5 ± 0.5 kg BW and the patients receiving 100% BCAA gained 0.45 ± 1.8 kg BW. The differences are not statistically significant. The three groups receiving amino acids, despite being in nitrogen equilibrium or mild positive nitrogen balance still lost weight (except for the almost negligible weight gain by the 100% BCAA group), and probably represent fat–tissue breakdown, although this is not certain.

Blood Chemistry

The changes in blood chemistries between preoperative levels and levels on postoperative day five are summarized in Table 4.

There were only minor, statistically nonsignificant changes in hemoglobin, hematocrit and white blood count between the different groups and between pre and postoperative values. Albumin levels dropped a mean of 0.7 g/dl in the 5% dextrose (0.7 ± 0.08) and the Freamine group (0.7 ± 0.1), dropped 0.8 ± 0.1 g/dl in the FO80 group, but only 0.1 ± 0.5 g/dl in the 100% BCAA group /p = ns).

The variations in BUN between the different groups and between pre- and postoperative values were all within normal limits, as were also all electrolyte levels.

Glucose levels increased by 8–19 mg/dl in the 5% dextrose, 22% and 35% BCAAs, and decreased by 16.3 ± 13.9 mg/dl in the 100% BCAA. However all levels are within normal limits and the differences are not statistically significant.

Plasma ammonia levels increased by 31.6 ± 24.6 μg/100 ml in the 5% dextrose, reaching a mean of 149 μg/100 ml which is mildly above normal levels (80–110 μg/100 ml). However there was no statistically significant difference between this group and the three groups receiving amino acids in which ammonia levels re-

TABLE 3. *Daily Nitrogen Balances (g N/24 Hours) in Four Groups of Postoperative Patients Infused with 5% Dextrose Alone or Together with 3% of Different Amino–Acid Formulations for Five Days Postoperatively (mean ± SEM)*

	5% Dextrose	22% BCAA	35% BCAA	100% BCAA
Day 1	−7.6 ± 1.2	2.2 ± 1.8*	−0.7 ± 0.8*	1.5 ± 1.7*
Day 2	−6.7 ± 1.4	1.1 ± 1.1*	1.6 ± 0.6*	0.06 ± 2.1*
Day 3	−6.8 ± 1.3	1.1 ± 0.9*	−1.1 ± 1.6*	2.9 ± 1.9†
Day 4	−6.0 ± 1.3	1.2 ± 0.8*	0.4 ± 0.9*	−1.3 ± 2.4†
Day 5	−5.7 ± 1.6	—	0.4 ± 2.6*	−0.7 ± 0.1*

*p < 0.001. †p < 0.01.

TABLE 4. *Blood Chemistry in 4 Groups of Patients Infused with 5% Dextrose Alone or 5% Dextrose with 3% Amino Acid Solutions Differing in Their BCAAs Concentrations. Preoperative Values are Compared with Values on Postoperative Day 5 During the Last Day of Infusion (mean ± SEM)*

	5% Dextrose		22% BCAA		35% BCAA		100% BCAA	
	Preoperative	Day 5	Preoperative	Day 5	Preoperative	Day 5	Preoperative	Day 5
BUN	13.5 ± 1.3	9.7 ± 0.6	11.8 ± 1.0	14.6 ± 2.8	16.9 ± 1.6	17 ± 1.3	22.2 ± 10.1	16.2 ± 3.3
Glucose	80.6 ± 4.5	108 ± 6.1	114 ± 13.6	126 ± 19.3	98.2 ± 7.7	127 ± 16	116 ± 14	99 ± 6.3
Ammonia	106.5 ± 10.1	149 ± 24	110.5 ± 16.5	103.4 ± 6.0	114 ± 13.3	115.6 ± 8.6	124.5 ± 30	104 ± [illegible]
Albumin	3.9 ± 0.1	3.2 ± 0.1	3.9 ± 0.2	3.2 ± 0.1	4.2 ± 0.1	3.4 ± 0.1	3.5 ± 0.5	3.4 ± 0.3
Bilirubin	0.4 ± 0.05	0.6 ± 0.1	0.6 ± 0.2	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.4 ± 0.09	0.4 ± 0.1
SGOT	23 ± 2.8	28 ± 4.0	21.4 ± 3.6	50.8 ± 15.6*	21.2 ± 5	62.4 ± 12.5*	22 ± 3.8	24.3 ± 2.0
Alk. Phosph.	4.5 ± 0.6	4.5 ± 0.5	5 ± 0.5	6.4 ± 1.4	4.5 ± 0.4	4.5 ± 0.6	3.6 ± 0.6	3.1 ± 0.4

* $p < 0.05$ (vs. preoperative levels).

mained stable within normal limits during the five day period of the infusion.

Among the liver function tests bilirubin and alkaline phosphatase levels did not change during the postoperative period, both remaining within normal levels in the four different groups. However, SGOT levels (normal 10–40 unit/ml) increased significantly during the infusion of both Freamine (32.5 ± 14.2 units/ml increase) and FO80 (40 ± 12.8 unit/ml increase). These increases in the Freamine and FO80 groups were both significant when compared to the corresponding SGOT levels in the 5% dextrose and 100% BCAA groups ($p < 0.05$).

Plasma Amino Acid Pattern

When the plasma amino acid patterns in the four different groups of patients studied are compared with normal plasma amino acid patterns the following changes are apparent (Fig. 2):

1) With minimal variations the amino acid patterns are similar to the normal pattern.
2) Mild elevation of glycine and proline in the Freamine and FO80 group of the phenylalanine and methionine in the Freamine group can be attributed to the high content of these amino acids in the infused solutions.
3) Branched chain amino acid levels were increased relative to their concentration in the infused solutions with Freamine showing mild, FO80 moderate and the 100% BCAA solution excessive increases in BCAA levels.
4) In the patients receiving the 100% BCAA solution (despite its being an unbalanced solution) the plasma amino acid pattern was near normal except

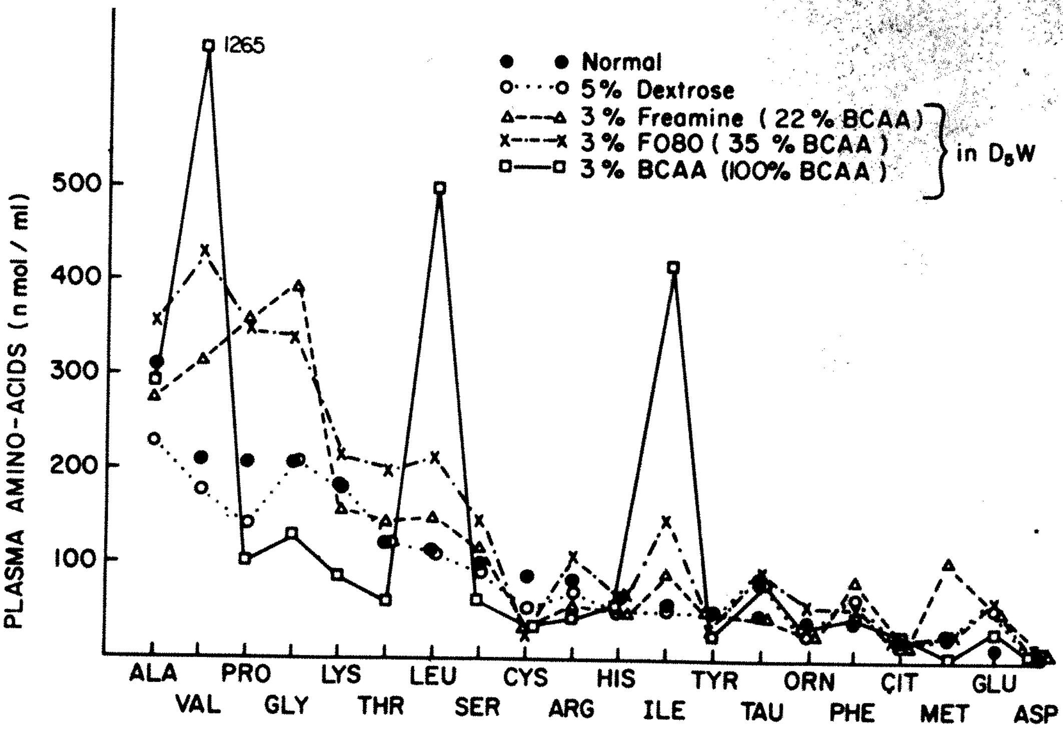


FIG. 2. Plasma amino acid patterns in 35 patients undergoing operative injury of moderate severity after five days of infusion of either 5% dextrose only or 5% dextrose with one of three 3% amino acid formulations differing in their branched chain amino acid concentrations.

P, 24, 761

for high BCAA levels and some mild statistically nonsignificant decrease in proline, glycine, lysine and threonine levels.

Discussion

The metabolic response to injury is characterized by an extensive and complex neuroendocrine activation resulting in rapid breakdown of muscle protein as substrate for energy production and gluconeogenesis and mobilization of body fat with the resultant well known postinjury negative nitrogen balance and weight loss. Skeletal muscle is the major site of protein breakdown after injury. Muscle protein breakdown in addition to being economically wasteful leads also to relative deficiency of essential amino acids like leucine, isoleucine and valine which are selectively and extensively utilized by the muscle as an energy source and substrate for gluconeogenesis. This relative deficiency might have deleterious results as to availability of essential amino acids for protein synthesis. The muscle breakdown itself affects all skeletal muscle so that at a certain stage if catabolism continues and no nutritional support afforded, vital functions like respiration, clearing of secretions and the like will be affected leading to death. In recent years, there has been increased interest in decreasing postinjury muscle catabolism by providing exogenous protein or amino acids with or without nonprotein calories to decrease catabolism. However only very limited attention was given to the qualitative amino acid requirements in the postinjury state.

The branched chain amino acids (BCAA) valine, leucine and isoleucine are the only essential amino acids that are principally oxidized by skeletal muscle.[1,2,10,12–14,21] The rate of oxidation of BCCAs in muscle is stimulated by fasting, hormonal influence, stress, diabetes, and other conditions associated with muscle protein wasting and negative nitrogen balance. Oxidation of the BCAAs supplies energy to the muscle and nitrogen for the glucose alanine cycle and muscle glutamine synthesis.[3,4,8,9,11,14,15,20] Recent *in vitro* experiments have also ascribed regulatory functions to the BCAAs. Fulks et al.[7] suggested that the BCAAs promoted protein synthesis and reduced protein degradation in a dose-dependent fashion. Odessey et al.[14] showed the BCAAs to inhibit net protein breakdown in muscle and to stimulate *de novo* synthesis of alanine and glutamine, thus offering energy substrate for liver, kidney and gut. Buse and Reid[2] suggested that leucine might act as a regulator of protein turnover in skeletal muscle by inhibiting protein degradation and promoting protein synthesis. In human studies Sapir et al.[16–18] achieved prolonged and improved nitrogen conservation during fasting by the administration of α–keto analogues of the BCAAs. Sherwin[19] infused leucin to fasting obese subjects with a resultant improvement in nitrogen balance but unchanged 3-methyl histidine excretion suggesting stimulation of muscle protein synthesis. Considering this information it seemed reasonable to assume that these three special properties of the BCAAs namely being an energy substrate for skeletal muscle, substrate for gluconeogenesis through alanine and glutamine and having a regulatory function in muscle protein degradation and synthesis, could be utilized for the reduction of postinjury protein catabolism.

In a series of experimental studies on rats which were subjected to injury consisting of laparotomy and jugular vein cannulation we were able to demonstrate that the nitrogen conserving quality of protein solutions in the postoperative period might be improved by increasing the amount of BCAAs.[6] Furthermore, the infusion of a solution consisting only of the three BCAAs resulted in nitrogen equilibrium and near normal plasma and muscle amino acid patterns, suggesting a complete shut-off of amino acid efflux from the muscle, the muscle depending completely on the exogenous supply of BCAAs to satisfy its metabolic requirement, resulting in nitrogen sparing. Additional experiments including using infusions of alanine alone suggest that only part of this improved nitrogen sparing quality of the BCAAs is due to production of alanine and its utilization for gluconeogenesis (unpublished data). In the present study four groups of patients undergoing operative injury of moderate degree were infused for 5 days starting immediately after surgery with isocaloric amounts of 5% dextrose, and three groups received equivalent amounts of protein which differ qualitatively, mainly in the BCAA concentration. All three amino acid solutions tested had a similar improved nitrogen conserving quality when compared to the group receiving 5% dextrose only.

The immediate postoperative infusion of 3% amino acid solutions in 5% dextrose resulted in nitrogen equilibrium or mild positive balance with no significant difference between the various solutions tested. Even the infusion of only the three BCAAs resulted in nitrogen equilibrium similar to the two other more balanced amino acid solutions. It thus seems that in the immediate postoperative or postinjury state the BCAAs by themselves, in pharmacologic amounts are capable of maintaining nitrogen equilibrium. Looking at the plasma free amino acid pattern in the four groups studied, essentially near normal patterns were maintained in all groups, including the 100% BCAA group (except for high BCAA levels). This near normal pattern in the group receiving a completely unbalanced amino acid solution containing only the three BCAAs can be explained by the complete cessation of amino acid efflux from the muscle, so that the muscle depends solely and completely on the exogenous supply of BCAAs to satisfy its metabolic requirements, similar to what Goldberg et al. reported in *in vitro* studies.[9] These results also are similar to those of Sapir et al.[17,18] who demonstrated temporary nitrogen equilibrium during starvation using the α-keto analogues of the BCAAs and to Sherwin's report[19] who demonstrated less negative nitrogen balance in fasted obese subjects infused with leucine.

The Freamine and FO80 groups lost weight during the five day study while the 100% BCAA group maintained its weight, this despite nitrogen equilibrium. It seems reasonable to assume that due to the hypocaloric solutions used in this study patients were utilizing fat tissue as a caloric source.

An interesting point which deserves brief mentioning is the change in liver function test with significant elevations in SGOT levels in the Freamine and FO80 groups. As only hypocaloric solutions were used and as both the 5% dextrose and 100% BCAA groups did not show any change in liver function tests these changes can be attributed to the infused amino acids (other than the BCAAs), as hypertonic glucose, which was not administered in these studies is most commonly incriminated.

Conclusions

Early nutritional support in the postoperative or postinjury state can result in nitrogen equilibrium or even mild positive nitrogen balance. The infusion of only the three BCAAs in the immediate postoperative period is as effective in respect to achieving nitrogen as other more balanced amino acid solution, probably equilibrium as other more balanced amino acid solution, probably by offering the muscle all it needs for its metabolic requirements and by complete shut off of amino acid efflux from the muscle. The nitrogen conserving quality of amino acid solutions in the postinjury period might be improved by increasing the amount of BCAAs.

References

1. Buse, M. G. and Buse, J.: Effect of Free Fatty Acids and Insulin on Protein Synthesis and Amino Acid Metabolism of Isolated Rat Diaphragms. Diabetes, 16:753, 1967.
2. Buse, M. G.. and Reid, M.: Leucine, a Possible Regulator of Protein Turnover in Muscle. J. Clin. Invest., 58:1251, 1975.
3. Felig, P., Pozefsky, T., Marliss, E. and Cahill, G. F.: Alanine: Key Role in Gluconeogenesis. Science, 167:1003, 1970.
4. Felig, P.L The Glucose Alanine Cycle. Metabolism, 22: 179, 1973.
5. Fischer, J. E., Rosen, H. M., Ebeid, A. M., et al.: The Effect of Normalization of Plasma Amino Acids on Hepatic Encephalopathy in Man. Surgery, 80:77, 1976.
6. Freund, H., Yoshimura, N., Lunetta, L. and Fischer, J. E.: The Role of the Branched Chain Amino Acids in Decreasing Muscle Catabolism in vivo. Surgery, 83:611, 1978.
7. Fulks, R. M., Li, J. B. and Goldberg, A. L.: Effects of Insulin, Glucose and Amino Acids on Protein Turnover in Rat Diaphragm. J. Biol. Chem., 250:280, 1975.
8. Garber, A. J., Karl, I. E. and Kipnis, D. M.: Metabolic Interrelationship and Factors Controlling Skeletal Muscle Protein Degradation and the Selective Synthesis and Release of Alanine and Glutamine. Clinical Nutrition Update—Amino Acids, American Medical Association, 1977, p. 10.
9. Goldberg, A. L. and Odessey, R.: Oxidation of Amino Acids by Diaphragms from Fed and Fasted Rats. Am. J. Physiol., 223:1384, 1972.
10. Manchester, K. L.: Oxidation of Amino Acid by Isolated Rat Diaphragm and the Influence of Insulin. Biochem. Biophys. Acta, 100:295, 1965.
11. Marliss, E. B., Aoki, T. T., Pozefsky, T., et al.: Muscle and Splanchnic Glutamine and Glutamate Metabolism in Postabsorptive and Starved Man. J. Clin. Invest., 50:814, 1971.
12. Miller, L. L.: The role of the liver and non-hepatic tissues in the regulation of free amino acid levels in blood, *In* Holden, J. J., (ed.) Amino Acid Pools. Amsterdam, 1962, Elsevier Publishing Co., p. 708.
13. Odessey, R. and Goldberg, A. L.: Oxidation of Leucine by Rat Skeletal Muscle. Am. J. Physiol., 223:1376, 1972.
14. Odessey, R., Khairallah, E. A. and Goldberg, A. L.: Origin and Possible Significance of Alanine Production by Skeletal Muscle. J. Biol. Chem., 249:7623, 1974.
15. Ruderman, N. B. and Berger, M.: The Formation of Glutamine and Alanine in Skeletal Muscle. J. Biol. Chem., 249:5500, 1974.
16. Sapir, D. G., Owen, O. E., Pozefsky, T. and Walser, M.: Nitrogen Sparing Induced by a Mixture of Essential Amino Acids Given Chiefly as their Keto-analogues During Prolonged Starvation in Obese Subjects. J. Clin. Invest., 54:974, 1974.
17. Sapir, D. G., Owen, O. E., Pozefsky, T. and Walser, M.: Nitrogen Sparing Induced by Keto-analogues of Essential Amino Acids. J. Clin. Invest., 53:70(a), 1974.
18. Sapir, D. G. and Walser, M.: Nitrogen Sparing Induced Early in Starvation by Infusion of Branched Chain Keto-acids. Metabolism, 26:301, 1977.
19. Sherwin, R. S.: Effect of Starvation on the Turnover and Metabolic Response to Leucine. J. Clin. Invest., 61:1471, 1978.
20. Wahren, J., Felig, P. and Hagenfeldt, L.: Effect of Protein Ingestion on Splanchnic and Leg Metabolism in Normal Men and in Patients with Diabetes Mellitus. J. Clin. Invest., 57: 987, 1976.
21. Young, V.: *In* Munro, H. N., (ed.) Mammalian Protein Metabolism, Vol. 4, New York, 1969, Academic Press, Inc., P. 585.

Use of Doppler Ultrasound in Intraoperative Localization of Intestinal Arteriovenous Malformation

MARC COOPERMAN, M.D., EDWARD W. MARTIN, JR., M.D., WILLIAM E. EVANS, M.D., LARRY C. CAREY, M.D.

From the Department of Surgery, The Ohio State University Hospitals, Columbus, Ohio

Precise localization of an intestinal arteriovenous malformation is essential for the complete resection of the lesion. Identification at operation can be difficult, and intraoperative angiography is not without complications. Blood flow within the small vessels of the bowel wall can be easily detected by Doppler ultrasonography, and arterial flow can be distinguished from venous flow. Intraoperative use of the Doppler ultrasound technique localized an AVM in the small intestine. Distinctive flow signals were present over the intestinal AVM which allowed it to be easily differentiated from adjacent normal intestine. Confirmation was secured by measuring the Po_2 of blood aspirated from the vein draining the involved segment and comparing it to the Po_2 from a vein draining an adjacent segment.

THE SUCCESSFUL OPERATIVE MANAGEMENT of patients with gastrointestinal hemorrhage secondary to intestinal arteriovenous malformations (AVMs) depends upon precise localization of the lesion at operation. Most of these lesions are located in the right colon,[7] and the operative approach is straightforward with right colectomy being curative. However, if the AVM is located in the small intestine, identification of the involved segment at operation can be difficult. The involved segment of intestine often appears normal, and transillumination of the bowel and intraoperative endoscopy may fail to identify the lesion. Angiography, which is often essential in the preoperative diagnosis of intestinal AVMs, has been advocated intraoperatively to precisely locate the lesion.[7] Intraoperative angiography, however, is cumbersome and not without complications. Recently, intraoperative mesenteric venous pressure and Po_2 measurement has been reported as a useful method of locating small intestinal AVMs at operation without requiring intraoperative arteriography.[5]

Doppler ultrasonography has proved to be a reliable method of detecting blood flow in small vessels and is widely used in the field of peripheral vascular disease. Blood flow within the small vessels of the bowel wall can also be easily detected by Doppler ultrasonography, and arterial flow is easily distinguished from venous flow. The technique is sufficiently sensitive and accurate to distinguish between viable and nonviable ischemic intestine and to enable selection of the optimum point of resection of nonviable intestine.[2,3,9]

We describe the successful use of Doppler ultrasound to precisely localize an AVM of the small intestine.

Case Report

A 55-year-old woman was admitted to The Ohio State University Hospitals for the fourth time for evaluation of guaiac-positive stools. Brief episodes of hemotochezia or melena had occurred in 1956, 1959, 1971, 1973, 1975, and 1977, and no cause had been found. The patient required multiple transfusions in the past. Numerous upper gastrointestinal small bowel and lower gastrointestinal barium studies were normal. A Meckel's scan was negative and the results of numerous sigmoidoscopies were normal. Four days before the current admission, the patient noted that her stools were again becoming dark. She denied abdominal pain, nausea, vomiting, anorexia, weight loss, diarrhea, or constipation. Her past medical history was otherwise negative.

Physical examination demonstrated that the patient was not in distress. Pulse was 76, blood pressure 120/70 mmHg, with no orthostatic drop, respirations 12 per min, and temperature 36.6°. A grade II/VI systolic ejection murmur was present at the apex and radiated to the left sternal border. The abdomen was soft and nontender. There were no masses or organomegaly. Bowel sounds were normal. Pelvic and rectal examinations were normal. The stool was guaiac-positive.

Laboratory values at hospital admission were as follows: Hemoglobin 12.4 g/100 ml; hematocrit 35.8%; sodium 139 meq/L; potassium 4.0 meq/L; BUN 15 mg/100 ml; and creatinine 0.7 mg/100 ml. Prothrombin time was 11.3 seconds, with the control 11.2 seconds. Partial thromboplastin time was 26 seconds. SGOT, SGPT, alkaline phosphatase, and bilirubin were normal. The electrocardiogram was normal.

Chest x-ray and plain abdominal films were normal. Oral cholecystogram demonstrated cholelithiasis. Upper gastrointestinal and small bowel x-rays were normal. Barium enema was normal. Colonoscopy was performed and results were entirely normal.

Reprint requests: Marc Cooperman, M.D., Department of Surgery, The Ohio State University Hospitals, 410 West 10th Avenue, Columbus, Ohio 43210.

Submitted for publication: February 12, 1979.

0003-4932/79/0700/0024 $00.65 © J. B. Lippincott Company

The patient's stools continued to be guaiac-positive. Arteriography was refused by the patient. It was decided to perform a laparotomy to attempt to identify the source of bleeding.

At operation the stomach, duodenum, and colon appeared normal. The small intestine was examined from the ligament of Treitz to the ileocecal valve. Transillumination of the small intestine showed an area of prominent vascularity in the terminal ileum approximately 15 cm proximal to the ileocecal valve. A 9MH$_2$ Doppler probe which had been gas-sterilized and calibrated to a Doppler flowmeter (Parks Electronics Model 806) was then placed on the bowel wall in the area of prominent vascularity. Distinctly increased arterial flow signals were present, compared to the signals from adjacent normal-appearing bowel. Recordings of the flow signals were made over the involved segment of intestine, adjacent small bowel, and the veins draining both areas. Blood was aspirated from the vein draining the involved segment using a 21 gauge needle. The Po$_2$ was 62 mmHg. The Po$_2$ of venous blood from an adjacent vein was 42 mmHg. The Doppler probe was then used to precisely determine the proximal and distal points at which abnormal signals were present. A three inch segment of small intestine was resected and an end-to-end anastomosis was performed. A cholecystectomy was done. The patient's postoperative course was uneventful. Histologic study of the resected ileum demonstrated a typical arteriovenous malformation. In the nine months since operation, the patient's stools have been guaiac-negative.

Results

Audible Doppler flow signals were distinctly abnormal over the AVM, compared to those over adjacent uninvolved intestine. A normal arterial Doppler tracing is shown in Figure 1. In comparison, the arterial tracing over the AVM (Fig. 2). shows distinctly increased amplitude. Normal arterial flow reversal is not seen. The tracing of the Doppler signal from the vein draining the AVM (Fig. 3) demonstrates high amplitude flow signals with arterial pulsations, compared to the normal venous flow signal which is nonpulsatile in nature.

The Po$_2$ in the vein draining the area of small intestine was 62 mmHg compared to a Po$_2$ of 42 mmHg in venous blood from an adjacent vein draining an uninvolved area of the bowel.

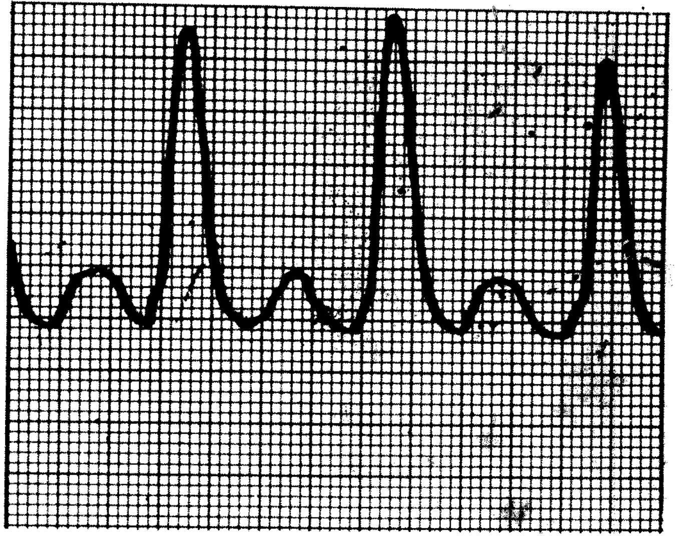


FIG. 2. Doppler tracing obtained over the intestinal AVM.

Discussion

Intestinal AVMs are coming to be recognized as a cause of gastrointestinal hemorrhage with increasing frequency.[1,4,6] These lesions pose difficult problems in diagnosis, as barium studies of the upper and lower gastrointestinal tracts are normal. The clinical picture most often encountered is that of a patient with multiple unexplained episodes of gastrointestinal blood loss.

Selective visceral arteriography has proved to be extremely useful in the diagnosis of these lesions. Studies have shown that in the presence of active bleeding of as little as 0.5 ml/min, the site of hemorrhage

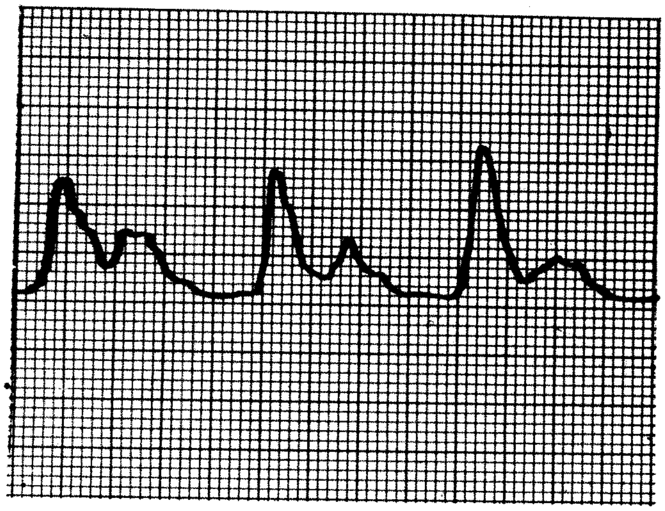


FIG. 1. Normal arterial tracing.

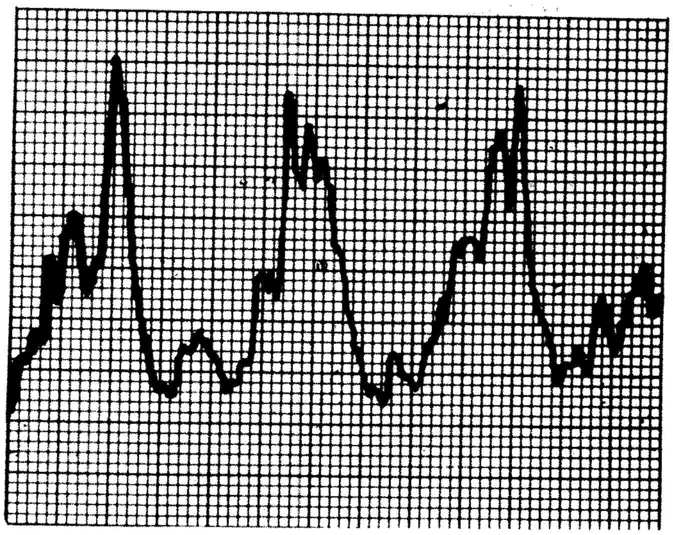


FIG. 3. Doppler tracing of vein draining the AVM.

can be located by this technique.[8] In the absence of active bleeding, a dilated feeding artery, a vascular tuft in the bowel, or early filling of a dilated mesenteric venous branch are radiographic signs of intestinal AVMs. If arteriography demonstrates that the AVM is located within the colon, operative treatment is straightforward and consists of resection of the involved segment of colon.

However, if arteriography demonstrates an AVM of the small intestine, intraoperative localization of the involved area of bowel may be difficult. The intestine may appear grossly normal, and transillumination of the bowel is frequently not helpful. The location of the AVM in reference to an easily identifiable vessel such as the ileocolic artery should be determined. At operation, the mesenteric vascular supply is exposed and by counting back from this reference point, the approximate area of involved intestine may be determined.

Doppler ultrasound equipment is relatively inexpensive, easily portable for use in the operating room, and already available in many hospitals. The Doppler probes are gas-sterilizable for intraoperative use. The tip of the sterile probe is coated with a sterile water-soluble gel, and is lightly applied at a 45° angle to the wall of the intestine as shown in Figure 4. It is important that only light pressure is applied to avoid compression of the small vessels within the intestinal wall. The technique is easily learned, and arterial and venous flow signals are readily detected within normal small and large bowel.

In the presence of an intestinal AVM, Doppler flow signals are abnormal over the involved segment of bowel. Blood flow is greatly increased, resulting in a distinctly increased audible arterial signal over the involved segment. Flow tracings demonstrate strikingly increased amplitude and loss of normal arterial flow reversal (Fig. 2). The arteriovenous shunting also results in an abnormal flow pattern in the vein draining the involved segment of intestine. The flow pattern is almost arterial in its configuration (Fig. 3).

Once the site of the intestinal AVM has been located by Doppler ultrasonography, the ultrasound findings can be confirmed by the presence of an elevated Po_2 in the vein draining the involved segment, compared to the Po_2 in adjacent mesenteric veins. In our patient, the venous Po_2 was 62 mmHg in the vein draining the AVM, compared to 42 mmHg in an adjacent mesenteric vein. This supports the previously reported usefulness of mesenteric venous pressure and Po_2 measurements in the localization of intestinal AVMs.[5]

The precise extent of the intestinal AVM can then be determined by Doppler ultrasound. The intestine is resected proximally and distally at the points where flow signals within the bowel wall are again normal. This technique will ensure complete resection of the AVM and will avoid an unnecessarily extensive resection of uninvolved intestine.

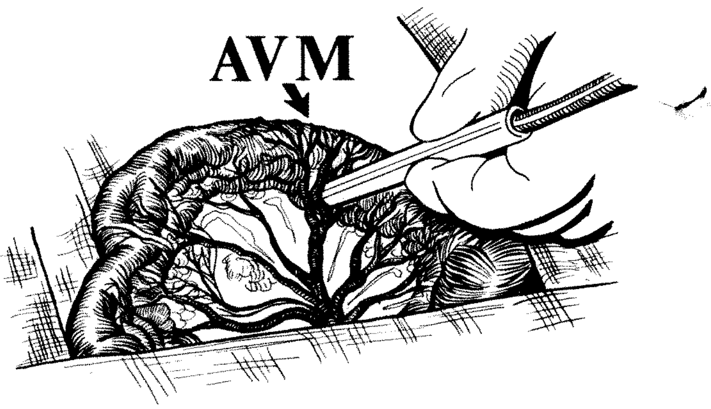


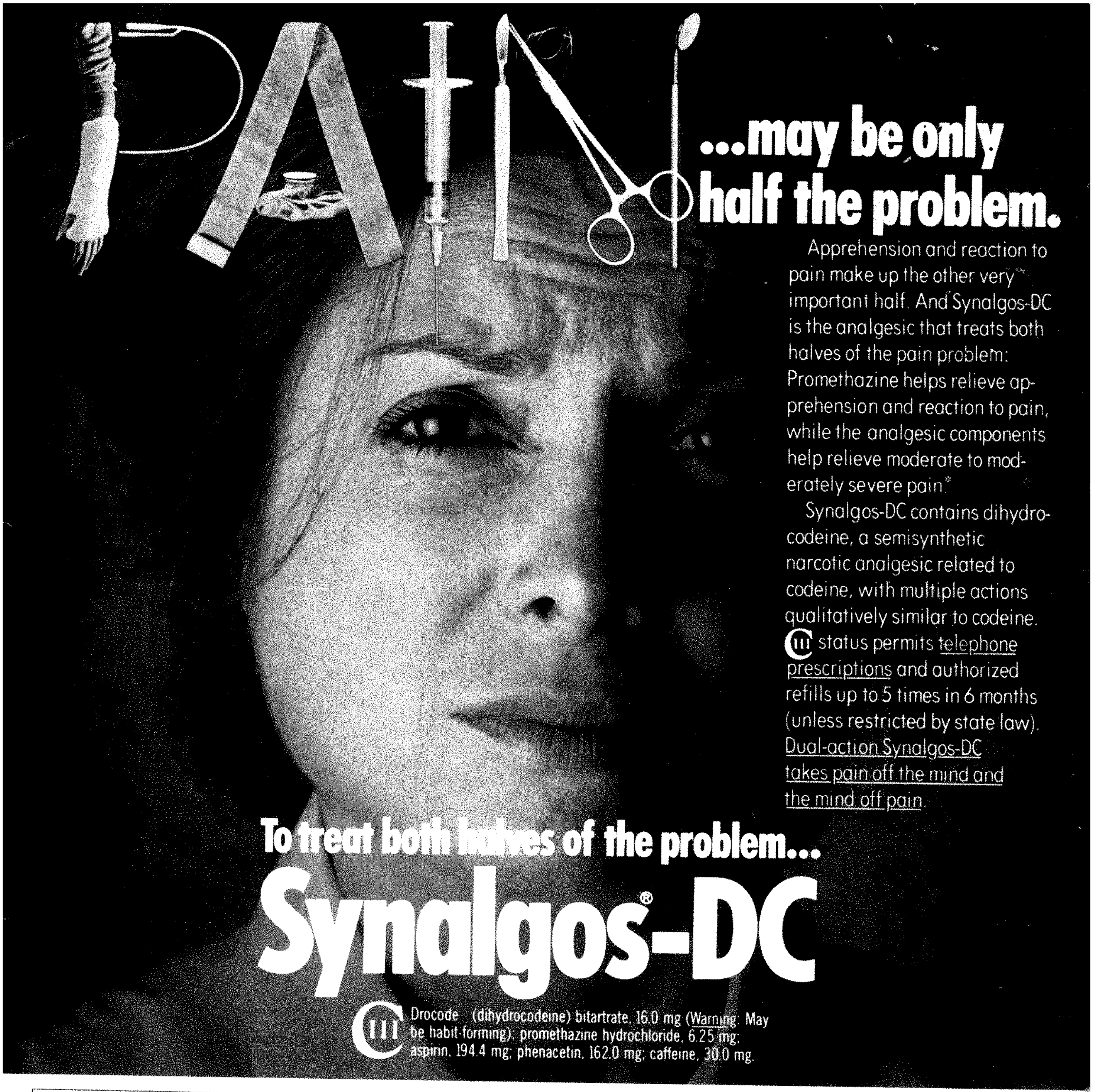
FIG. 4. The Doppler probe is applied intraoperatively to the intestinal wall.

Summary

Doppler ultrasonography is a sensitive method of detecting blood flow within the wall of the intestine. In the presence of an intestinal AVM, flow signals over the involved segment of intestine are distinctly increased in amplitude and abnormal in character. The use of Doppler ultrasonography permits rapid, precise intraoperative localization of the site and extent of intestinal AVMs.

References

1. Cooperman, A. M., Kelly, K. A., Bernatiz, P. E., et al.: Arteriovenous Malformation of the Intestine. Arch. Surg. 104: 284, 1972.
2. Cooperman, M., Pace, W. G., Martin, E. W., Jr., et al.: Determination of Viability of Ischemic Intestine by Doppler Ultrasound. Surgery, 83:705, 1978.
3. Cooperman, M., Martin, E. W., Jr., Evans, W. E. and Carey, L. C.: Assessment of Anastomotic Blood Supply in Operations upon the Colon by Doppler Ultrasound. Surg. Gynecol. Obstet. (in press).
4. Cricklow, R. W., Mosenthal, W. T., Spiegel, P. K., et al.: Arteriovenous Malformations of the Bowel: An obscure Cause of Bleeding. Am. J. Surg. 129:440, 1975.
5. Evans, W. E., O'Dorisio, T. M., Milnar, W., et al: Intraoperative Localization of Intestinal Arteriovenous Malformations. Arch. Surg., 113:410, 1978.
6. Heald, R. J. and Ray, J. E.: Vascular Malformations of the Intestine: An Important Cause of Obscure Gastrointestinal Hemorrhage. South. Med. J., 67:33, 1974.
7. Margulis, A. R., Heinbecke, P. and Bernard, H. R.: Operative Arteriography in the Search for the Site of Bleeding in Unexplained Gastrointestinal Hemorrhage. A Preliminary Report. Surgery, 48:534, 1960.
8. Nusbaum, M., Baum, S. and Blakemore, W. S.: Clinical Experience with the Diagnosis and Management of Gastrointestinal Hemorrhage by Selective Mesenteric Catheterization. Ann. Surg., 170:506, 1969.
9. Wright, C. B. and Hobson, R. W.: Prediction of Intestinal Viability using Doppler Ultrasound Technics., Am. J. Surg. 129:642, 1975.



...may be only half the problem.

Apprehension and reaction to pain make up the other very important half. And Synalgos-DC is the analgesic that treats both halves of the pain problem: Promethazine helps relieve apprehension and reaction to pain, while the analgesic components help relieve moderate to moderately severe pain.*

Synalgos-DC contains dihydrocodeine, a semisynthetic narcotic analgesic related to codeine, with multiple actions qualitatively similar to codeine. C III status permits telephone prescriptions and authorized refills up to 5 times in 6 months (unless restricted by state law). Dual-action Synalgos-DC takes pain off the mind and the mind off pain.

To treat both halves of the problem...

Synalgos®-DC

C III Drocode (dihydrocodeine) bitartrate, 16.0 mg (Warning: May be habit-forming); promethazine hydrochloride, 6.25 mg; aspirin, 194.4 mg; phenacetin, 162.0 mg; caffeine, 30.0 mg.

*__INDICATIONS:__ Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective for the relief of moderate to moderately severe pain in those situations where the physician wishes to add a mild sedative effect. Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Hypersensitivity to dihydrocodeine, promethazine, aspirin, phenacetin.

WARNINGS: Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

Drug Dependence: Dihydrocodeine can produce drug dependence of the codeine type and therefore has the potential of being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of dihydrocodeine, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, dihydrocodeine is subject to the provisions of the Federal Controlled Substances Act. **Usage in Ambulatory Patients:** Dihydrocodeine and promethazine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Synalgos-DC should be cautioned accordingly. **Interactions with other Central Nervous System Depressants:** Patients receiving other narcotic analgesics, general anesthetics, other phenothiazines, tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Synalgos-DC may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Patients who have demonstrated a hypersensitivity reaction (e.g. blood dyscrasia, jaundice) with a phenothiazine should not be reexposed to any phenothiazine, including Synalgos-DC, unless in the judgment of the physician the potential benefits of the treatment outweigh the possible hazards. **Usage in Pregnancy:** Reproduction studies have not been performed in animals. There is no adequate information on whether this drug may affect fertility in human males and females or has a teratogenic potential or other adverse effect on the fetus. **Usage in Children:** Since there is no experience in children who have received this drug, safety and efficacy in children have not been established.

PRECAUTIONS: Phenacetin has been reported to damage kidneys when taken in large amounts for a long time. Promethazine should be administered cautiously to patients with cardiovascular or liver disease. Synalgos-DC should be given with caution to certain patients such as the elderly or debilitated, and those with hypothyroidism, Addison's disease and prostatic hypertrophy and urethral stricture.

ADVERSE REACTIONS: The most frequently observed reactions include lightheadedness, dizziness, drowsiness, sedation, nausea, vomiting, constipation, pruritus, skin reactions, and rarely, hypotension.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. Synalgos-DC is given orally. The usual adult dose is 2 capsules every 4 hours as needed for pain.

DRUG INTERACTIONS: The CNS depressant effects of Synalgos-DC may be additive with that of other CNS depressants. See Warnings. Aspirin may enhance the effects of anticoagulants and inhibit the uricosuric effects of uricosuric agents.

Consult direction circular before prescribing.

IVES LABORATORIES INC.
New York, NY 10017
Dedicated to improving the quality of life, through Medicine®
Ives

ATLAS OF APPLIED VASCULAR SURGERY

By KIYOSHI INOKUCHI, M.D.,
and AKIRA KUSABA, M.D.

Here is a unique and timely atlas text describing the wide variety of diseases and lesions that have been successfully treated through vascular anastomoses performed with a new stapling instrument originated and perfected by Dr. Inokuchi.

The extensive experiences of the authors with vessel suturing equipment have extended the use of these instruments beyond the repair and reconstruction of vessels, to other areas of surgery. For example, use of the Inokuchi stapling instrument has made possible the free transplantation of intestine as a reconstruction of the cervical esophagus.

A highlight of the book is a discussion of the many problems and difficulties which arise in portacaval shunt for portal hypertension. The authors have realized success in this operation and describe a new technique—left gastric venous-caval shunt.

This highly descriptive book contains details on the design of the Inokuchi vascular stapler and step-by-step instructions on its use and applications. Many of the operations performed utilizing the device are discussed, describing the techniques used and giving case histories.

198 pages / 301 illustrations, including 68 photographs.
11 in color / 21 Tables / 1975 / $57.00

Lippincott

J. B. Lippincott Company
East Washington Square • Phila., Pa. 19105

Please send me:

☐ ATLAS OF APPLIED VASCULAR SURGERY $57.00

Name ____________________

Address ____________________

City ____________ State ________ Zip ________

☐ Payment enclosed Save postage & handling ☐ Charge and bill me Plus postage & handling

Also available at your medical bookstore AS 7/79

Mefoxin® IV/IM
(Cefoxitin Sodium | MSD)

Indications: Treatment of serious infections caused by susceptible strains of the designated microorganisms in the following diseases:
LOWER RESPIRATORY TRACT INFECTIONS, including pneumonia and lung abscess, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), other streptococci (excluding enterococci, e.g., *Strep. faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Klebsiella* species, *Hemophilus influenzae*, and *Bacteroides* species.
URINARY TRACT INFECTIONS caused by *E. coli*, *Klebsiella* species, *Proteus mirabilis*, indole-positive *Proteus* (i.e., *P. morganii*, *P. rettgeri*, and *P. vulgaris*), and *Providencia* species.
INTRA-ABDOMINAL INFECTIONS, including peritonitis and intra-abdominal abscess, caused by *E. coli*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,[‡] and *Clostridium* species.
GYNECOLOGICAL INFECTIONS, including endometritis and pelvic cellulitis, caused by *E. coli*, *Bacteroides* species including the *B. fragilis* group,[‡] *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species, and group B streptococci.
SEPTICEMIA caused by *Strep. pneumoniae* (formerly *D. pneumoniae*), *Staph. aureus* (penicillinase and non-penicillinase producing), *E. coli*, *Klebsiella* species, and *Bacteroides* species including the *B. fragilis* group.[‡]
BONE AND JOINT INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing).
SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing), *Staph. epidermidis*, streptococci (excluding enterococci, e.g., *Strep. faecalis*), *E. coli*, *P. mirabilis*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,[‡] *Clostridium* species, *Peptococcus* species, and *Peptostreptococcus* species. Although appropriate culture and susceptibility studies should be performed, therapy may be started while awaiting these results.

Contraindications: Previous hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. GIVE WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Precautions: The total daily dose should be reduced in patients with transient or persistent reduction of urinary output due to renal insufficiency because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses. As with other antibiotics, prolonged use may result in overgrowth of nonsusceptible organisms; repeated evaluation of the patient's condition is essential. If superinfection occurs, take appropriate measures. Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.
Interference with Laboratory Tests—As with cephalothin, high concentrations (>100 mcg/ml) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction and produce false increases of modest degree in creatinine levels reported; serum samples should not be analyzed for creatinine if withdrawn within 2 hours of cefoxitin administration. A false-positive reaction for glucose in urine has been observed with CLINITEST[§] reagent tablets.
Pregnancy—In women of childbearing potential, weigh anticipated benefit against possible risks.
Nursing Mothers—Cefoxitin is excreted in human milk in low concentrations.
Infants and Children—Safety and efficacy in infants and children have not yet been established.

Adverse Reactions: The most common adverse reactions have been local reactions following intravenous or intramuscular injection. Other adverse reactions have been encountered infrequently. *Local Reactions*—Thrombophlebitis with intravenous administration; pain, induration, and tenderness after intramuscular injections. *Allergic Reactions*—Rash, pruritus, eosinophilia, fever, and other allergic reactions. *Gastrointestinal*—Nausea, vomiting, and diarrhea. *Blood*—Transient leukopenia, neutropenia, and hemolytic anemia; a positive direct Coombs test may develop in some individuals, especially those with azotemia. *Liver Function*—Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase. *Renal Function*—Elevations in serum creatinine and/or blood urea nitrogen levels.

Note: In group A beta-hemolytic streptococcal infections, therapy should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated. Intramuscular injections should be well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel.

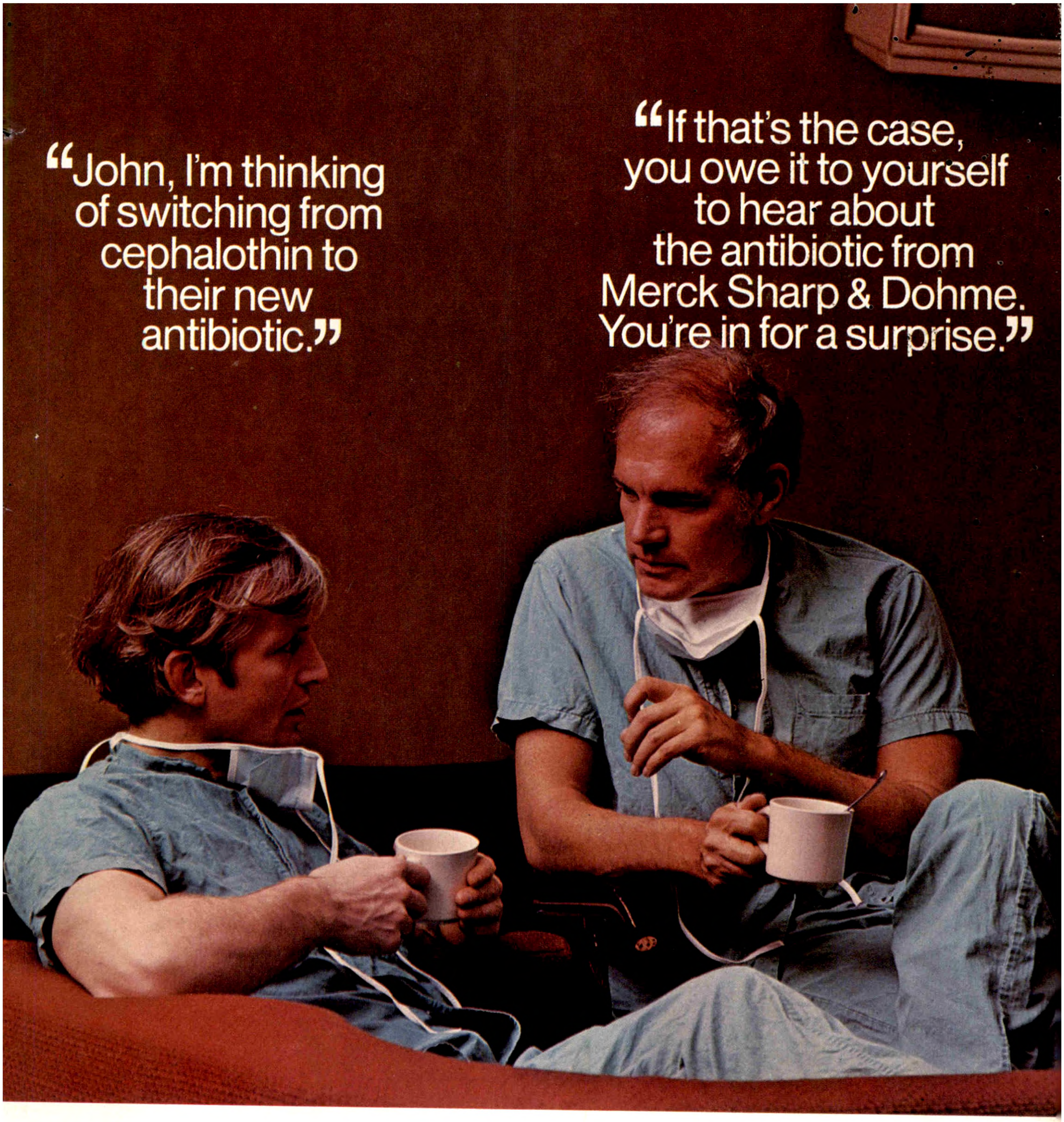
How Supplied: Sterile cefoxitin sodium in vials and infusion bottles containing 1 gram or 2 grams cefoxitin equivalent.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

[‡] *B. fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*
[§] Registered trademark of Ames Company, Division of Miles Laboratories, Inc.

MSD
MERCK
SHARP
DOHME

J9MF10R2(105)


"John, I'm thinking of switching from cephalothin to their new antibiotic."
"If that's the case, you owe it to yourself to hear about the antibiotic from Merck Sharp & Dohme. You're in for a surprise."

the first cephamycin derivative(1)

Mefoxin® IV/IM

(Cefoxitin Sodium | MSD)

VIALS, containing 1 gram and 2 grams cefoxitin equivalent

(1) MEFOXIN is often referred to as a cephamycin in the scientific literature.

Copyright © 1979 by Merck & Co., Inc.

Get the full story. . .
from your MSD
professional
representative

MSD
MERCK
SHARP&
DOHME

For a brief summary of prescribing information, please see facing page.

For ulcerative proctitis patients who

CORTIFOAM®
(hydrocortisone acetate 10% rectal foam)

Contains hydrocortisone acetate 10% as the sole active ingredient in 20 GMs of a foam containing propylene glycol, ethoxylated stearyl alcohol, polyoxyethylene-10-stearyl ether, cetyl alcohol, methyl and propyl parabens, triethanolamine, water and inert propellants.

Each application delivers approximately 900 mg. of foam containing 80 mg. of hydrocortisone (90 mg. of hydrocortisone acetate)

Clinical pharmacology: CORTIFOAM provides topical administration of an anti-inflammatory corticosteroid as adjunctive therapy of ulcerative proctitis.

Indications: CORTIFOAM is indicated as adjunctive therapy in the topical treatment of ulcerative proctitis of the distal portion of the rectum in patients who cannot retain hydrocortisone or other corticosteroid enemas.

Direct observations of methylene blue-containing foam have shown staining no higher than 10 centimeters into the rectum.

Contraindications: Local contraindications to the use of intrarectal steroids include obstruction, abscess, perforation, peritonitis, fresh intestinal anastomoses, extensive fistulas and sinus tracts.

Tuberculosis (active, latent or questionably healed), ocular herpes simplex and acute psychosis are usually considered absolute contraindications to the use of corticosteroids. Relative contraindications include active peptic ulcer, acute glomerulonephritis, myasthenia gravis, osteoporosis, diverticulitis, thrombophlebitis, psychic disturbances, pregnancy, diabetes, hyperthyroidism, acute coronary disease, hypertension, limited cardiac reserve, and local or systemic infections, including fungal or exanthematous diseases. Where these conditions exist, the expected benefits from steroid therapy must be weighed against the risks involved in its use. Pregnancy is a relative contraindication to corticosteroids, particularly during third trimester. If corticosteroids must be administered in pregnancy, watch newborn infant closely for signs of hypoadrenalism, and administer appropriate therapy if needed.

Warning: Do not insert any part of the aerosol container into the anus. Contents of the container are under pressure, but not flammable. Do not burn or puncture the aerosol container. Store at room temperature—not over 120°F.

Because CORTIFOAM is not expelled, systemic hydrocortisone absorption may be greater from CORTIFOAM than from corticosteroid enema formulations. If there is no evidence of clinical or proctologic improvement within two or three weeks after starting CORTIFOAM therapy, or if the patient's condition worsens, discontinue the drug.

Precautions: Steroid therapy should be administered with caution in patients with severe ulcerative disease because these patients are predisposed to perforation of the bowel wall. Where surgery is imminent, it is hazardous to wait more than a few days for a satisfactory response to medical treatment. General precautions common to all corticosteroid therapy should be observed during treatment with CORTIFOAM. These include gradual withdrawal of therapy to allow for possible adrenal insufficiency and awareness to possible growth suppression in children. Patients should be kept under close observation, for, as with all drugs, rare individuals may react unfavorably under certain conditions. If severe reactions or idiosyncrasies occur, steroids should be discontinued immediately and appropriate measures instituted. Do not employ in immediate or early postoperative period following ileorectostomy.

Adverse reactions: Corticosteroid therapy may produce side effects which include moon face, fluid retention, excessive appetite and weight gain, abnormal fat deposits, mental symptoms, hypertrichosis, acne, ecchymosis, increased sweating, pigmentation, dry scaly skin, thinning scalp hair, thrombophlebitis, decreased resistance to infection, negative nitrogen balance with delayed bone and wound healing, menstrual disorders, neuropathy, peptic ulcer, decreased glucose tolerance, hypopotassemia, adrenal insufficiency, necrotizing angiitis, hypertension, pancreatitis and increased intraocular pressure. In children, suppression of growth may occur. Increased intracranial pressure may occur and

can't retain the steroid enema...

Frequently your ulcerative proctitis patient can't retain the steroid enema: when the patient needs to be ambulatory; when the patient is in the early stages of therapy; when a steroid enema triggers the onset of tenesmus, or when sphincter control is weak.

Now there's an alternative to the retention enema—Cortifoam® (hydrocortisone acetate 10%) rectal foam. With Cortifoam, the steroid is kept in contact with the inflamed mucosa by a muco-adhesive foam base. Unlike retention enemas, Cortifoam can be administered at any time convenient to the patient in just 30 seconds—even while standing. Following administration, Cortifoam requires no lengthy period of reclining, no struggle to retain medication. And it usually won't leak or stain even in active patients. "This form of treatment is better tolerated since it does not provoke the tenesmus or urgency that often accompany a fluid enema."*

Finally, Cortifoam is more economical per application than commercially-available steroid enemas.

So when you need an alternative for ulcerative proctitis patients who can't retain steroid enemas, now you can prescribe one—Cortifoam.

*Korelitz, B.I.: *Hospital Medicine* 14:8-34, March, 1978

Reed & Carnrick/Kenilworth, New Jersey 07033

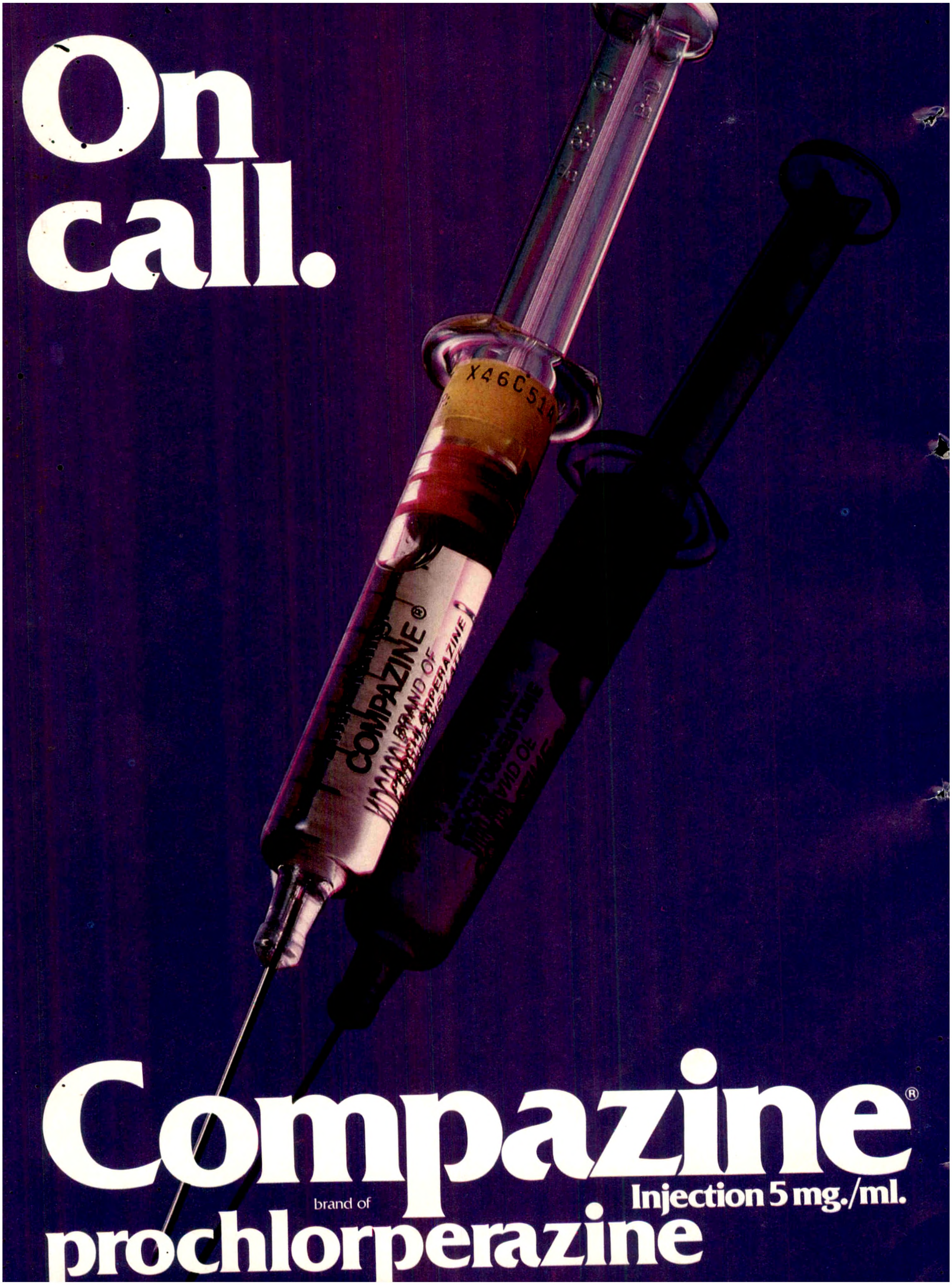
The easy-to-retain alternative.

Cortifoam®
(hydrocortisone acetate 10%) rectal foam

possibly account for headache, insomnia and fatigue. Subcapsular cataracts may result from prolonged usage. Long-term use of all corticosteroids results in catabolic effects characterized by negative protein and calcium balance. Osteoporosis, spontaneous fractures and aseptic necrosis of the hip and humerus may occur as part of this catabolic phenomenon. Where hypopotassemia and the other symptoms associated with fluid and electrolyte imbalance call for potassium supplementation and salt-poor or salt-free diets, these may be instituted and are compatible with diet requirements for ulcerative proctitis.

Administration and dosage: Usual dose is one applicatorful once or twice daily for two or three weeks, and every second day thereafter, administered rectally. The patient direction package with the applicator describes how to use the aerosol container and applicator. Satisfactory response usually occurs within five to seven days marked by a decrease in symptoms. Symptomatic improvement in ulcerative proctitis should not be used as the sole criterion for evaluating efficacy. Sigmoidoscopy is also recommended to judge dosage adjustment, duration of therapy and rate of improvement.

How supplied: CORTIFOAM is supplied in an aerosol container with a special rectal applicator. Each applicator delivers approximately 900 mg. of foam containing approximately 80 mg. of hydrocortisone as 90 mg. of hydrocortisone acetate. The aerosol container will deliver a minimum of 14 applications.



On call.
X46C514
COMPAZINE®
BRAND OF PROCHLORPERAZINE
Compazine®
brand of
prochlorperazine
Injection 5 mg./ml.

For prompt control of severe nausea and vomiting.

- **Unsurpassed antiemetic action**
- **12 dosage forms and strengths**

Compazine®

brand of

prochlorperazine

NOTE: Do not use 'Compazine' in pediatric surgery.

Not recommended for children under 20 lbs. or 2 years of age. In children with acute illnesses or dehydration, use only under close supervision.

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indications: Management of the manifestations of psychotic disorders; management of psychoneurotic patients displaying primarily symptoms of moderate to severe anxiety and tension; and for control of severe nausea and vomiting.

'Compazine' has not been shown effective in the management of behavioral complications in patients with mental retardation.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants; bone marrow depression; pediatric surgery.

Warnings: The extrapyramidal symptoms which can occur secondary to 'Compazine' may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g., Reye's syndrome or other encephalopathy. The use of 'Compazine' and other potential hepatotoxins should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

Avoid using in patients hypersensitive (e.g., blood dyscrasias or jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days' therapy. Prochlorperazine may intensify or prolong the action of other C.N.S. depressants. Not recommended for children under 20 pounds or 2 years of age.

Use in pregnancy only when potential benefits outweigh hazards.

Precautions: The antiemetic action of 'Compazine' may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as intestinal obstruction, brain tumor and Reye's syndrome (See WARNINGS). Postoperative aspiration of vomitus has occurred in a few surgical patients who received prochlorperazine as an antiemetic. Deep sleep and coma have been reported, usually with overdosage. Patients on long-term therapy, especially high doses, should be evaluated periodically for possible adjustment or discontinuance of drug therapy. **In children with acute illnesses or dehydration, use only under close supervision.**

Adverse Reactions: Drowsiness, dizziness, amenorrhea, blurred vision, skin reactions. Hypotension. Cholestatic jaundice, leukopenia, agranulocytosis. Fatty changes in the liver have been observed in a few patients who died while receiving the drug (no causal relationship has been established). Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, persistent tardive dyskinesia. Contact dermatitis is a possibility with concentrate and injectable forms.

Other adverse reactions reported with Compazine (prochlorperazine, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., severe hypotension in mitral insufficiency or pheochromocytoma).

Grand mal convulsions; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat and organophosphorus insecticides; dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, inhibition of ejaculation; reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; pancytopenia, thrombocytopenic purpura, eosinophilia; biliary stasis; lactation, galactorrhea, gynecomastia, menstrual irregularities, false-positive pregnancy tests; photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis; asthma, laryngeal edema; angioneurotic edema, anaphylactoid reactions; peripheral edema; reversed epinephrine effect; hyperpyrexia; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes have been reported, but relationship to myocardial damage is not confirmed. Discontinue long-term, high-dose therapy gradually.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported, but no causal relationship has been established.

Supplied: Tablets – 5, 10 and 25 mg., in bottles of 100; Spansule® capsules – 10, 15, 30 and 75 mg., in bottles of 50; Injection – 5 mg./ml. in 2 ml. ampuls, 10 ml. vials, and 2 ml. disposable syringes; Suppositories – 2-1/2, 5 and 25 mg.; Syrup – 5 mg./5 ml.; Concentrate (intended for institutional use only) – 10 mg./ml.; Single Unit Packages of 100 (intended for institutional use only) – 5 and 10 mg. tablets; 10, 15 and 30 mg. 'Spansule' capsules.

SK&F
a SmithKline company

Smith Kline &French Laboratories
Philadelphia, PA

When pain can't wait

Talwin® LACTATE

brand of
pentazocine lactate injection, NF (IV)

30 mg parenterally q. 3 to 4 hours.

Pain relief proven:

Clinical proof of efficacy was determined in a wide variety of disease entities.*

Cardiovascular: Of 142 patients, 84% had excellent to good relief.

Gastrointestinal: Of 134 patients (including those with malignancy), 90% had excellent to good relief.

Malignancy: Of 214 patients, 82% had excellent to good relief.

Urology: Of 232 patients, 72% had excellent to good relief.

Miscellaneous: Of 245 patients, 80% had excellent to good relief.

*All doses of Talwin (30 mg Talwin lactate was the most common dose used). Data on file at Winthrop Laboratories.

Over 3/4 billion parenteral doses used worldwide.

Talwin has shown infrequent occurrence of some morphine-like adverse effects such as:

- Severe respiratory depression
- Hypotension
- Constipation
- Urinary retention

While others such as nausea and vomiting are more common.

RARELY REPORTED REACTIONS are those of a psychiatric nature. Even the most acute CNS reactions—hallucinations (usually visual)—have cleared spontaneously within a period of hours. Such patients should be closely observed. In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain. *There have been instances of psychological and physical dependence on Talwin in patients with a history of drug abuse. Such patients should be closely supervised when long-term therapy is contemplated.* **See important paragraph on drug dependence on next page.**

See important product information including warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations, a brief summary of which follows.

Potent—Dependable—Analgesic

Talwin® LACTATE

brand of
pentazocine lactate injection, NF ⓒⅣ

Relieves pain of a moderate to severe nature.

Please consult full prescribing information before prescribing. A summary follows: TALWIN is intended for the relief of moderate to severe pain. 30 mg is usually as effective an analgesic as morphine 10 mg or meperidine 75 to 100 mg. The duration of analgesia may sometimes be less than that of morphine. Analgesia usually occurs within 15 to 20 minutes after intramuscular or subcutaneous injection and within 2 to 3 minutes after intravenous injection. TALWIN is a weak narcotic antagonist with sedative activity. TALWIN may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Hypersensitivity to pentazocine.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on TALWIN in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral TALWIN has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral TALWIN with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for TALWIN in the treatment of the pentazocine abstinence syndrome should be avoided. There have been rare reports of possible abstinence syndromes in newborns after prolonged use of TALWIN during pregnancy.*

In prescribing parenteral TALWIN for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of TALWIN is preferable for chronic administration.

Tissue Damage at Injection Sites. Severe sclerosis of the skin, subcutaneous tissues, and underlying muscle have occurred at the injection sites of patients who have received multiple doses of pentazocine lactate. Constant rotation of injection sites is, therefore, essential. In addition, animal studies have demonstrated that TALWIN is tolerated less well subcutaneously than intramuscularly.

Head Injury and Increased Intracranial Pressure. TALWIN may elevate cerebrospinal fluid pressure. This may be markedly exaggerated in the presence of head injury, intracranial lesions, and a preexisting increase in intracranial pressure. TALWIN may obscure the clinical course of patients with head injuries. TALWIN should be used with extreme caution in such patients and only if its use is deemed essential.

Usage in Pregnancy. Safe use of TALWIN during pregnancy (other than labor) has not been established. Although no teratogenic or embryotoxic effects have been reported in animals, TALWIN should be administered to pregnant patients (other than labor) only when potential benefits outweigh possible hazards; and cautiously in labor of women delivering prematurely.

Acute CNS Manifestations. In therapeutic dosage, rarely, transient hallucinations (usually visual), disorientation, and confusion may occur. Observe such patients carefully and check vital signs. Use caution if the drug is reinstituted since the acute CNS manifestations may recur.

Usage in Children. Not recommended under the age of 12.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Myocardial Infarction. Caution should be exercised in the intravenous use of pentazocine for patients with acute myocardial infarction accompanied by hypertension or left ventricular failure. Data suggest that intravenous administration of pentazocine increases systemic and pulmonary arterial pressure and systemic vascular resistance in patients with acute myocardial infarction.

Precautions: The possibility that TALWIN may cause respiratory depression should be considered in treating patients with bronchial asthma. TALWIN should be used with caution and in low dosage to patients with respiratory depression, severely limited respiratory reserve, respiratory obstruction, cyanosis, renal or hepatic dysfunction. Caution should also be used with patients prone to convulsive disorders and those about to undergo biliary surgery. Patients previously given narcotics, including methadone, may experience withdrawal symptoms after receiving TALWIN.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Dermatologic Reactions: Soft tissue induration, nodules, and cutaneous depression can occur at injection sites. Ulceration (sloughing) and severe sclerosis of the skin and subcutaneous tissues (and, rarely, underlying muscle) have been reported after multiple doses.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received TALWIN during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face, toxic epidermal necrolysis.

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg intravenously or 60 mg intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg.

See Warnings in package insert as to recommended sites and routes of administration. Use subcutaneously only when necessary because of possibility of severe tissue damage at injection sites. For frequent intramuscular injections, note need for rotation of sites as described.

Patients in Labor. A single, intramuscular 30 mg dose has been most commonly administered.

CAUTION: TALWIN should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: Oxygen, parenteral naloxone, intravenous fluids, vasopressors, assisted or controlled ventilation, and other supportive measures should be employed as indicated.

How Supplied: *Uni-Amp®—Individual unit dose ampuls of 1 ml (30 mg)* NDC 0024-1924-04, *1½ ml (45 mg)* NDC 0024-1925-04, *and 2 ml (60 mg)* NDC 0024-1926-04 in boxes of 25.

Uni-Nest™ ampuls of 1 ml (30 mg) NDC 0024-1924-14, *1½ ml (45 mg)* NDC 0024-1925-14, *and 2 ml (60 mg)* NDC 0024-1926-14 in boxes of 25.

Each 1 ml contains pentazocine lactate equivalent to 30 mg base and 2.8 mg sodium chloride, in water for injection.

Carpuject® Sterile Cartridge-Needle Units, *1 ml (30 mg)* NDC 0024-1917-02, *1½ ml (45 mg)* NDC 0024-1918-02, *and 2 ml (60 mg)* NDC 0024-1919-02, all in 2 ml cartridge, boxes of 10. Each 1 ml contains pentazocine lactate equivalent to 30 mg base, 1 mg acetone sodium bisulfite, and 2.2 mg sodium chloride, in water for injection.

Multiple-dose vials of 10 ml NDC 0024-1916-01, boxes of 1. Each 1 ml contains pentazocine lactate equivalent to 30 mg base, 2 mg acetone sodium bisulfite, 1.5 mg sodium chloride, and 1 mg methylparaben as preservative, in water for injection.

Winthrop
90 PARK AVENUE
NEW YORK, N.Y. 10016

The Effects of Metoclopramide on Postoperative Ileus

A Randomized Double-blind Study

EUGENE D. DAVIDSON, M.D., THEODORE HERSH, M.D., RICHARD A. BRINNER, M.D.,
STEPHEN M. BARNETT, M.D., LAWRENCE P. BOYLE, M.D.

Metoclopramide or placebo was administered postoperatively in a randomized, double-blind fashion to 115 patients undergoing laparotomy. The effect of metoclopramide on postoperative adynamic ileus (PAI) was evaluated. The patients were stratified into two groups: Group A—those with laparotomy without a gastrointestinal anastomosis or ostomy procedure, and group B—those with laparotomy undergoing an anastomosis or ostomy procedure. Metoclopramide reduced nausea and emesis postoperatively. However, the only significant effect on postoperative adynamic ileus was an earlier return to tolerance of solid foods in the patients in Group A.

From the Departments of Surgery and Medicine (Digestive Diseases), Emory University School of Medicine, Atlanta, Georgia

POSTOPERATIVE ADYNAMIC ILEUS (PAI) is an expected concomitant of celiotomy. Efforts directed toward elimination or amelioration of ileus have been unsuccessful. Intestinal pacing via peroral gastric electrode stimulation[15] and transcutaneous electrical stimulation[18] have not reduced PAI. Pharmacologic stimulation via D-pantothenyl alcohol has also been ineffective.[14] Neostigmine has been used widely for prevention of PAI without good documentation of its efficacy.

Metoclopramide, a drug derived from procaine amide, has been shown to be an effective antiemetic agent with properties of enhancing gastrointestinal motility.[6,9,17] The drug stimulates gastric contractions and thereby accelerates gastric emptying.[7,11] The drug stimulates smooth muscle contraction in the small intestine which accelerates intestinal transit time.[10] Metoclopramide exerts minimal effect on colonic motility, though some *in vitro* and *in vivo* studies show stimulation of the colon with metoclopramide.[1,7] This study set out to examine the efficacy and safety of metoclopramide compared to placebo in the prevention of postoperative ileus.

Metoclopramide has been used extensively in Europe for prevention of PAI. Controlled studies by Breivak and Lind,[4] Makrigiannis and Gaca[13] and Friis[8] support its routine use in the patients undergoing celiotomy. Banke[2] did not show a reduction in time to first defecation in a double blind study of patients post-vagotomy and pyloroplasty given postoperative metoclopramide.

Methods

Study Population

One hundred and twenty-five adult patients were enrolled in the study after careful explanation of the procedure, the medication and risks involved. All patients signed an approved institutional informed consent. One hundred and fifteen patients completed the study and were available for statistical analysis. The patients were categorized in two groups: Group A consisted of 58 patients undergoing abdominal surgery where no entry into the stomach, duodenum, small intestine or large intestine was made. Group B consisted of 57 patients where gastrointestinal entry, anastomosis or suture was performed. The patient population characteristics are listed in Table 1. All selected patients underwent intra-abdominal surgery with a total anesthesia time of more than one and one-half hours duration. All surgical patients were interviewed for the study except for those with Parkinson's disease or known seizure disorders, patients with known hypersensitivity to procaine amide or other related drugs, patients with severe renal, cardiac or hepatic disease and patients taking parasympathomimetic drugs or phenothiazines.

The patients were assigned to either the placebo or treatment group in a predetermined, randomized

---

Reprint requests: Eugene D. Davidson, M.D., Veterans Administration Hospital (Atlanta) 1670 Clairmont Road, Decatur, Georgia 30033.

Submitted for publication: January 29, 1979.

0003-4932/79/0700/0024 $00.70 © J. B. Lippincott Company

double-blind fashion. The code could only be broken if untoward reactions occurred. The patients were administered either metoclopramide 10 mg, or an intramuscular sterile buffer solution on the evening of surgery and at 7:30 a.m., 11:30 a.m. and 5:30 p.m. on the days following surgery. Similarly, the test medication was given orally in tablets when oral fluids were tolerated. Medication was stopped when solid food was tolerated and/or defecation had occurred.

The intraoperative course, recovery room time and postoperative symptoms were recorded for each patient. The following items were assessed three times daily at morning, noon and night in each patient each day until termination of the study: abdominal distention, abdominal cramping, nausea, vomiting, passage of flatus, passage of stool, presence or absence of bowel sounds, tolerance of oral fluids, tolerance of solid foods, nasogastric drainage, intravenous fluids given, drugs administered, and presence or absence of significant postoperative complications. In addition, all patients had temperature, blood pressure, pulse rate and measurement of abdominal girth recorded daily.

The data were examined and computer coded and separated into two categories for analytic purposes. The first category consisted of the presence or absence of nausea, vomiting, abdominal cramping, abdominal distention and need for an indwelling nasogastric tube. The data were analyzed by both the number of patients with or without symptoms and the total frequency of the symptoms. These data were analyzed for the day of surgery and the first two postoperative days only while the patients were all receiving injectable drug.

The second category analyzed the length of time until tolerance of oral fluids and of solid food, the timing of the first occurrence of passage of flatus and of stool and the appearance of bowel sounds in relationship to the time of surgery. These data were analyzed by considering the total number of doses administered, whether parenteral or oral.

The statistical methods included log linear analysis of nominal qualitative data by the method of maximum likelihood, the chi-square test of difference of proportions and Fischer's exact test. Data were analyzed for both population groups. Ten patients were eliminated from the study: three refused to participate postoperatively and seven either died or had life threatening complications requiring removal from the protocol. One hundred and fifteen patients completed the protocol and their data were analyzed.

TABLE 1. *Mean Age, Range of Age and Sex of Study Patients*

	Group A		Group B	
	Age (Range)	M/F	Age (Range)	M/F
Placebo	52.1 yrs (21–84)	13/16	49.7 yrs (30–77)	15/13
Metoclopramide	48.8 yrs (20–81)	14/15	52.8 yrs (19–81)	16/13
Total subjects		27/31		31/26

TABLE 2. *Nausea and Emesis During the First Two and One-half Postoperative Days*

		Metoclopramide	Placebo	Significance
Group A				
Nausea	Present	14	10	ns
	Absent	15	19	
Emesis	Present	1	7	$p < 0.05$
	Absent	28	22	
Group B				
Nausea	Present	5	12	$p < 0.05$
	Absent	24	16	
Emesis	Present	1	1	ns
	Absent	28	27	

Results

Table 2 shows the effect of the test drug on the occurrence of postoperative nausea and emesis. The number of patients having nausea in Group B in the two day postsurgical period was significantly less than patients in the placebo group ($p < 0.05$). When both Groups A and B were pooled, the overall number of reports of nausea was statistically less in the metoclopramide treated patients than in the placebo group ($p < 0.05$). Emesis was significantly reduced only in the Group A patients receiving metoclopramide when compared to placebo ($p = 0.027$ single tailed test).

Table 3 shows that in Group A patients the time until tolerance of solid food was significantly lower in the metoclopramide treated group than in the placebo treated group. This difference did not appear in Group B patients. The number of patients achieving food tolerance is less than the number of patients in each group. This discrepancy occurred because in some

TABLE 3. *Total Drug Doses (*i.e. *Time) Until Tolerance of Solid Food in Group A and Group B Patients*

		Median Doses—10 Less Than or Equal to Median Number of Doses	Greater Than Median Number of Doses
Group A	Metoclopramide	24	4
	Placebo	14	10
		$p < 0.05$	
Group B	Metoclopramide	7	17
	Placebo	10	13
		ns	

patients the study medication was discontinued at first defecation prior to resumption of a solid food diet.

There were no other statistically significant differences in the other variables measured. Abdominal pain and cramping, return of bowel sounds, passage of flatus and stool and tolerance of fluids showed no significant differences in Group A or Group B patients between metoclopramide and placebo treated groups. The findings on physical examination, temperature, pulse, blood pressure, laboratory determinations including electrolytes, were not different in placebo or drug treated patients.

In the metoclopramide treated group, side effects reported included one patient with marked and eight with mild sedation. Mild sedation, however, was also noted in six patients who received the placebo. Restlessness was reported in three patients on metoclopramide and two patients on placebo. Dystonia was recorded for three patients on placebo but was not noted in cases taking metoclopramide. No other untoward symptoms were attributable to either test drug. The overall incidence of adverse reactions was 10.4% in the metoclopramide group and 9.6% in the placebo treated group.

Discussion

This study confirms previous studies in demonstrating a statistically significant difference for reduction in the frequency of postoperative nausea and vomiting in patients receiving injectable metoclopramide.[6,9,17] The aforementioned studies showed that metoclopramide was effective in reducing postoperative nausea and vomiting after single dose administration, particularly in patients who were concomitantly receiving narcotic analgesics. The present study, where patients received the injectable drug over a period of two and one-half days postoperatively, demonstrated significant reduction in the frequency of vomiting in Group A patients and in nausea in Group B patients. There was also an overall significant reduction in nausea when both groups were pooled.

Metoclopramide exerts an antiemetic action by its activity on the vomiting center and on the chemoreceptive trigger zone. The drug also enhances gastric motility and improves gastric emptying, which may further contribute to its antiemetic properties. A combination of these two effects, central and gastric, should be additive in reducing postoperative vomiting.

This study does not support the European studies[4,8,13] concerning the effects of metoclopramide on postoperative ileus. With the exception of the significant reduction in the time until tolerance of solid foods in patients undergoing abdominal operation without entry into the gastrointestinal tract, there was no significant effect exerted by metoclopramide on any of the other parameters measured. No other indicators of ileus achieved significance. Abdominal distention, abdominal girth, cramping pain, toleration of oral fluids, and the passage of the first stool were similar in both drug and placebo treated patients in both Group A and Group B. Although the drug did not significantly reduce the period of symptomatic postoperative ileus, none of the 115 patients experienced prolonged postoperative ileus. We have used metoclopramide successfully for the treatment of an established ileus, but the effect of the drug cannot be isolated from the general postoperative care measures instituted concurrently. Kronberger[12] has reported excellent results using metoclopramide in treating prolonged PAI.

Electrophysiologic studies have shown that abdominal laparotomy initially produces a loss of spike potentials and contractions in the entire intestine and these return within 12–24 hours after surgery.[5,16] In the experimental animal, coordinated propulsion of intestinal contents down the gut is, however, inhibited for periods of three to seven days after laparotomy.[16] Gastric pacing via peroral electrode could not be expected to diminish PAI in the small intestine and perhaps most importantly the colon would not be stimulated. The right colon may be the site of maximum delay in PAI: Neostigmine can produce gut contraction but does not restore coordinated propulsion and may be dangerous if any mechanical component of obstruction is present.

Metoclopramide may increase gut contraction by acting as a dopamine antagonist.[3] It does not produce spasm and it does restore coordinated contraction in the gastrointestinal tract. The lack of effect on PAI may reflect the drug's inability to stimulate the colon *in vivo*. The study by Friis[8] would suggest that higher doses of metoclopramide may be needed to reduce PAI.

Conclusions

Metoclopramide, an agent which enhances gastrointestinal motility and acts centrally as an antiemetic, was given to 115 patients undergoing major abdominal surgery. Patients were stratified into those with and those without gastrointestinal suture or anastomosis. The major effects of metoclopramide when compared to placebo included a significant reduction in postoperative emesis in patients without gut anastomosis. There was a significant reduction in nausea in patients with gastrointestinal anastomoses and in the total frequency of nausea in both groups.

Overall postoperative ileus was unaffected by metoclopramide with the exception of a statistically significant earlier return to solid food diet in patients not undergoing gastrointestinal anastomosis. All other parameters indicative of ileus remained the same for metoclopramide and placebo treated patients.

Acknowledgment

The authors wish to thank Dr. V. A. Vokac, A. H. Robins Co., Richmond, Va., for providing metoclopramide and Dr. J. R. Amerson, Dr. W. C. McGarity, Dr. G. D. Perdue and Dr. R. B. Smith, III, for providing study patients.

References

1. Banke, L.: Research on the action of metoclopramide in the gastrointestinal tract. *In* Modern Gastroenterology (Proceedings of VIII International Congress on Gastroenterology, Prague, July, 1968) 571 (Schattauer, Stuttgart, 1969).
2. Banke, L., Malstrom, J. and Heltberg, J.: The influence of Metopramide and Neostigmine Upon Early Postvagotomy Motor Disturbances. Scand. J. Gastroenterol., 7:33, 1972.
3. Baumann, H. W., McCallum, R. W. and Sturdevant, R. A. L.: Metoclopramide: A Possible Antagonist of Dopamine in the Esophagus of Man. Gastroenterology, 70:862, 1976.
4. Breivik, H. and Lind, B.: Anti-emetic and Propulsive Peristaltic Properties of Metoclopramide. Br. J. Anaesth., 43:400, 1971.
5. Carmichael, M. J., Weisbrodt, N. W. and Copeland, E. M.: Effect of Abdominal Surgery on Intestinal Myoelectric Activity in the Dog. Am. J. Surg., 133:34, 1977.
6. Clark, M. M. and Storrs, J. A.: The Prevention of Postoperative Vomiting After Abortion: Metoclopramide. Br. J. Anaesth., 41:980, 1969.
7. Eisner, M.: Effect of Metoclopramide on Gastro-intestinal Motility in Man. Am. J. Dig. Dis., 16:409, 1971.
8. Friis, T.: Effect of Primperan Versus Neostigmine Upon the Gastro-Intestinal Tract During the Postoperative Period. Ugesk. Laeger, 133:91, 1971.
9. Handley, A. J.: Metoclopramide in the Prevention of Postoperative Nausea and Vomiting. Br. J. Clin. Pract., 21:460, 1967.
10. James, W. B. and Hume, R.: Action of Metoclopramide on Gastric Emptying and Small Bowel Transit Time. Gut, 9:203, 1968.
11. Johnson, A. G.: The Action of Metoclopramide on Human Gastroduodenal Motility. Gut, 12:421, 1971.
12. Kronberger, L.: Treatment of Prolonged Gastrointestinal Paresis. Deutsch. Med. J., 20:459, 1969.
13. Makrigiannis, D. and Gaca, A.: Use of Paspertin in Urology. Zeitschr. Therapie, 6:338, 1968.
14. Polacek, M. A., Yount, L., Carpenter, B., et al.: Clinical Evaluation of D-pantothenyl Alcohol in Prevention of Postoperative Ileus. Am. J. Surg., 108:19, 1964.
15. Quast, D. C., Beall, A. C., Jr. and DeBakey, M. E.: Clinical Evaluation of the Gastrointestinal Pacer. Surg. Gynecol. Obstet., 120:35, 1965.
16. Smith, J., Kelly, K. A. and Weinshilboum, R. M.: Pathophysiology of Postoperative Ileus. Arch. Surg., 112:203, 1977.
17. Tornetta, F. J.: Clinical Studies with the New Antiemetic Metoclopramide. Anesth. Analg., 48:198, 1969.
18. VanderArk, G. D. and McGrath, K. A.: Transcutaneous Electrical Stimulation in Treatment of Postoperative Pain. Am. J. Surg., 130:338, 1975.

Typhoid Perforation of the Bowel

Experiences in 78 Cases

F. C. EGGLESTON, M.D., F.A.C.S., B. SANTOSHI, M.S., C. M. SINGH, M.S., PH.D.

From the Department of Surgery, Christian Medical College and Hospital, Ludhiana, Punjab, India

Seventy-eight patients ranging from four to 65 years of age were treated for typhoid perforation of the bowel. Sixty-one patients (78%) were males. The average time from perforation to admission was 56 hours. The mortality rate was 32% and was adversely influenced by the duration of illness, duration of perforation, shock, uremia, encephalopathy and fecal peritonitis. Forty-nine patients were treated by closure of the perforation, resection or miscellaneous procedures; the other 29 by closure of the perforation combined with an end-to-side ileotransverse colostomy. Although mortality was the same in both groups, those undergoing bypass had a significantly smoother postoperative course.

TYPHOID FEVER CONTINUES to be a major problem through much of the world, particularly in tropical climates. The introduction of Chloramphenicol resulted in a dramatic decrease in the overall mortality from this condition, but did not, unfortunately, reduce the incidence of perforation. The management of patients with this complication has been debated in recent years and attention focused upon the role of surgery. It is our purpose to review our experience with 78 patients treated for typhoid perforation and to discuss a new surgical approach which, although it has not altered mortality, has lowered morbidity.

Materials and Methods

The case records of all patients undergoing operative procedures because of typhoid perforation from January, 1963 through December, 1978 were reviewed. There were 78 patients in this study, the criteria for inclusion being isolation of Salmonella typhi from the blood or stool, a positive Widal reaction or typical operative findings in conjunction with histological examination.

Results

Incidence of Perforation

The overall incidence of perforation was 5.3% of 1,470 patients discharged with a diagnosis of typhoid fever. It is of interest to note that this incidence has been rising significantly over the years ($p < 0.001$) (Table 1).

Age and Sex

The youngest patient was four years old and the oldest 65 (Table 2) with 63% in the second and third decades of life.

Sixty-one, (78%) of the patients were males. Among all the patients treated for typhoid fever in this study period, males made up 65.9%. This difference was significant ($x^2 = 5.6$, $p < 0.02$).

Seasonal Incidence

Although patients with typhoid perforation were seen throughout the year, over half were admitted during the four months (July to October) following the onset of the monsoon.

Duration of Illness

Approximately half of the perforations occurred during the second and third weeks of illness (Table 3). Those who had symptoms for more than four weeks were generally in a state of relapse. Mortality was significantly less in patients ill less than one week ($x^2 = 5.49$, $p < 0.02$).

Duration of Perforation

In 64 patients it was possible to determine with accuracy the duration of perforation (Table 4). Mortality was significantly lower in those with perforations of less than 48 hours ($x^2 = 6.08$, $p < 0.02$).

Signs and Symptoms

The majority of patients presented with fever and malaise, often associated with bowel symptoms. They

---

Reprint requests: Dr. F. C. Eggleston, Professor and Head, Department of Surgery, Christian Medical College and Hospital, Ludhiana, Punjab 141008, India.

Submitted for publication: February 23, 1979.

0003-4932/79/0700/0031 $00.75 © J. B. Lippincott Company

TABLE 1. *Incidence of Perforation*

Years	Typhoid Cases Hospitalized	Perforations	Percentage
1963–67	422	7	1.7
1968–72	410	17	4.1
1973–78	638	54	8.5
	1,470	78	5.3

$\chi^2 = 24.9$, $p < 0.001$.

TABLE 3. *Duration of Illness*

Weeks	Cases	Deaths	Mortality Per Cent
less than 1	15	1	7
1–2	25	8	32
2–3	17	9	53
3–4	4	1	25
4+	17	6	35
	78	25	32

had noted a sudden increase in abdominal pain often associated with vomiting and distension at time of perforation. However, 14 were unaware of any specific time at which perforation occurred.

On examination, findings were remarkably similar, with signs of toxemia and "acute abdomen." All the patients had abdominal rigidity. Hyperresonance was present over the liver in 70% of the patients and paralytic ileus was noted in 68%. Fifteen patients were in shock, eight (53%) of whom died.

Laboratory Investigations

Thirty-two of 41 patients in whom abdominal x-rays were taken had pneumoperitoneum. Total leukocyte count varied from 1,300 to 26,000 per mm^3 with a mean of 8,200. Fourteen patients had a leukocyte count below 5,000 while 24 had a leukocytosis greater than 10,000. Blood culture was done in 46 patients and was positive in 14. *S. typhi* was found in six and in the remaining patients *E. coli*, candida, staphylococci, klebsiella or psuedomonas were grown. Widal reaction was positive in 45 cases.

Previous Treatment

Twenty-seven patients had previously received incomplete treatment for typhoid or were under treatment in the hospital at the time of perforation. Eight of these patients (30%) died. An additional 22 patients gave a history of having received antibiotics other than chloramphenicol or ampicillin.

Admission Diagnosis

In 63 patients (81%) the diagnosis on admission was typhoid perforation. In five others it was considered in the differential diagnosis. The remaining 10 patients, however, were never suspected of having a typhoid perforation. In six, the diagnosis was ruptured appendix with peritonitis; in three, intestinal obstruction; and in one, acute cholecystitis.

Treatment

Patients were resuscitated as rapidly as possible and operated on without delay. Laparotomy was done in all but one patient who had septicemia and was moribund. In him, abdominal drainage was done under local anesthesia and a laparotomy was planned if his condition improved. However, he died three hours later.

Operative Findings

Peritonitis was present in all patients and was "fecal" in 15, of whom none (60%) died. In 52 of the 53 cases in whom peritoneal culture was done, pathogenic bacteria were found: *E. coli* in 48, klebsiella in 24 and other organisms in 16. In no case was *S. typhi* isolated.

In 74 patients open perforations were present. These were solitary in 67, while six patients has two perforations and one multiple perforations. In one patient the perforation was sealed off; and in two there was gangrene of the involved bowel. All perforations were on the antimesenteric border of the ileum except one

TABLE 2. *Age and Sex of Patients*

Years	Male	Female	Total
0–9	7	0	7
10–19	14	7	21
20–29	25	3	28
30–39	6	3	9
40–49	8	4	12
50+	1	0	1
	61	17	78

TABLE 4. *Duration of Perforation*

	Cases	Deaths	Mortality Per Cent
less than 24 hrs.	10	1	10
24–48 hrs.	14	2	14
48–72 hrs.	22	7	32
72–96 hrs.	12	5	42
96+ hrs.	6	4	67
unknown	14	6	42
	78	25	32

TABLE 5. *Operative Procedures*

	Cases	Deaths	Mortality Per Cent
Simple closure	43	13	30
Ileotransversostomy	29	9	31
Ileal resection	3	2	67
Drainage or unknown	3	1	33

which was in the cecum. Half were within 20 cm of the ileocecal junction.

Operative Procedures

In the earlier part of this series, simple closure of the ulcer was the most commonly done procedure (Table 5). This was generally done in two layers after freshening the edges. Since 1975, we have begun a prospective trial of an end-to-side ileotransverse colostomy in addition to closure of the ulcer. This has now been done in 29 of the last 39 cases.

The group undergoing ileotransverse colostomy (bypass group) was compared with those undergoing other procedures. No differences were found in age, duration of illness, duration of perforation or incidence of shock. The only significant difference was a higher incidence of fecal peritonitis in the bypass group (31% vs 12%) ($x^2 = 4.1$, $p < 0.05$).

Complications

Sixty-three (81%) of the patients had one or more complication (Table 6). For the most part these were related to sepsis in one form or another. When analyzed according to whether a bypass procedure or another procedure was done, it was apparent that although the total complication rate was the same, the incidence of major wound complications and fecal fistulae was significantly less in those having a bypass ($x^2 = 5.47$, $p < 0.02$).

Three patients developed fatal uremia. Two others had jaundice, one transiently. Chloramphenicol was used extensively and two patients had nonfatal leukopenia.

TABLE 6. *Postoperative Complications*

	No Bypass (49)	Bypass (29)
None	8	7
Major wound infection or dehisence	12	2
Fecal fistula	7	2
Chest infection	16	8
Septicemia	4	5
Intra-abdominal abscess	5	0
Encephalopathy	5	1
Minor wound infection	5	10
Miscellaneous	12	9

TABLE 7. *Duration of Hospitalization in Survivors*

	No bypass (33)		Bypass (20)	
	Cases	Per Cent	Cases	Per Cent
2 weeks	3	9	4	20
2–3 weeks	9	27	9	45
3–4 weeks	6	18	3	15
4–5 weeks	8	24	2	10
5+ weeks	7	21	2	10

Eight patients returned with late complications. Four had subacute obstruction managed without further surgery. Two developed incisional hernias, one (in the bypass group) had a mild short bowel syndrome for which treatment was refused. One patient had been discharged with a fecal fistula that was nearly closed. He was reoperated on at another hospital and returned to us with a massive and eventually fatal fistula.

Mortality

Overall mortality, including the single late death, was 32%. This mortality was unrelated to the operative procedure done, but was definitely influenced by several factors, namely, the duration of disease prior to admission (Table 3), the duration of the perforation prior to surgery (Table 4), the presence of shock, uremia or encephalopathy, the presence of fecal peritonitis, endotoxemia and the development of postoperative fecal fistulae. In the majority of patients it was impossible to ascribe a single cause of death other than that of severe sepsis.

Hospital Stay

In patients surviving, the mean duration of postoperative hospitalization was 28.1 days. However, patients having a bypass procedure had an average hospitalization of 23.1 days compared to 31.5 days for those not having such a bypass. A significantly greater number of survivors went home within three weeks of surgery when a bypass was done ($x^2 = 4.1$, $p < 0.02$) (Table 7).

Discussion

The frequency of enteric perforation in typhoid fever has been reported variously from 0.8%[17] to 18%.[3] This may represent variations in the virulence of the organism or differences in sociological circumstances. The rising incidence of perforation among hospitalized patients (Table 1) suggests that patients with typhoid fever are being treated by private doctors in the home more frequently than previously and are only referred to the hospital for complications.

Typhoid fever produces hyperplasia of the reticuloendothelial system with necrosis and ulceration of the gut, generally limited to Peyer's patches in the terminal ileum, although the jejunum and cecum may occasionally be involved. Cecal ulcers are smaller than those in the ileum and rarely perforate.[12] The number and size of the ulcers is unrelated to the severity of the clinical symptoms.[4] Characteristically these ulcers do not produce peritoneal reaction before they perforate, and even after perforation, peritoneal response seems to be delayed and the ulcer is rarely found to be sealed off at operation.[6,11] In contradistinction to other perforations, the omentum does not migrate to the site. Bowel contents, therefore, continue to empty into the peritoneal cavity.

These perforations, generally single, appear as "punched out" holes on the anti-mesenteric border of the bowel. Huckstep[9] and Olurin et al.[14] claim that the bowel around the perforation is friable, a finding with which we do not agree.[20] Sutures hold well, but healing is impaired and complications common.

Typhoid perforation is rare under the age of five or over the age of 50.[3,9,13] More than 50% of patients are in the second or third decade of life and males predominate in a three to one ratio.[3,13]

Perforation may be accompanied by a sudden sharp pain or an abrupt increase in abdominal symptoms associated with vomiting, distension and constipation. However, in patients who have been ill for a long time, the symptoms may be much more subtle and the exact time of perforation difficult to determine.[8] Abdominal tenderness and toxemia are constant findings. Bowel sounds are frequently absent and x-ray examination demonstrates pneumoperitoneum in about half the patients.[5,7] Shock carries a bad prognosis.

Enteric perforation is best managed surgically. Huckstep[9] in 1960 recommended a nonoperative approach (albeit with certain exceptions). He mentioned that the contamination from these perforations was "virtually sterile." Few workers today agree with him,[19] although some have suggested avoiding surgery in very late cases.[13] The consistent operative findings in our patients make us feel that surgery is mandatory. In 96% either an open perforation or gangrene was found, rarely with any signs of localization, even in late cases. Furthermore, all but one of 53 peritoneal cultures (98%) demonstrated one or more pathogenic organism even though 34 (64%) of this group had received preoperative antibiotics. Not to remove this purulent (and often frankly fecal) material and prevent further soilage of the peritoneal cavity just does not make sense. Accordingly, we have operated upon all of our patients.

In addition to an adequate peritoneal toilet, the correct management of the perforation itself is essential. Probably as a result of the known high incidence of postoperative complications, a wide variety of operative procedures have been utilized. These include simple closure of the perforation,[2,6,20] local wedge resection of the ulcer,[20] purse string closure,[1] resection of the affected ileum[5,11,20] sometimes combined with right hemicolectomy,[20] side-to-side ileotransverse colostomy,[15] temporary ileostomy[18] or ileostomy through the perforation.[10]

All operative procedures reported have been followed by a high complication rate. Archampong,[2] for example, had a 52% incidence of wound sepsis. The combination of massive peritonitis and poor patient resistance is the obvious cause for this. Reperforation or perforation from another ulcer is followed by peritonitis and fecal fistula and generally a fatal outcome.[7,20] It is difficult to differentiate the two unless reoperation is performed.[14] This procedure is frequently impossible because of the poor condition of the patient or associated wound sepsis. Accordingly, since 1975 we have performed an end-to-side ileotransverse colostomy in the majority (75%) of our cases. It is our belief that the ideal procedure for these patients should be one which is relatively bloodless and quick and one which protects against fecal contamination should the perforation reopen or a new perforation at another site occur. End-to-side ileotransverse colostomy carried out well proximal to the perforation should do this. It is now our procedure of choice.

While our mortality rate has not changed with the introduction of this procedure, morbidity has ($p < 0.02$). This has been particularly evident in the reduction of major wound infections, dehiscences and fecal fistulae. The most convincing proof has been in the significantly ($p < 0.02$) shorter period of hospitalization in survivors (Table 7).

Mortality varies greatly. Kim et al.[11] reported a 9.9% mortality rate, whereas Dickson and Cole[7] reported 62%. It appears that this is related to the delay in presentation of the patient, it being 38 hours in the former series and three days in the latter. In our series, the average duration was 56 hours and mortality 32%.

Until typhoid fever is eliminated by improved sanitation and immunization programs, surgeons will be confronted with its complications. Of these, enteric perforation is the most common and lethal. Only prompt recognition and urgent surgical intervention will improve results.

References

1. Abdel-menein, R. I.: Surgical Management of Perforated Typhoid Ulcer. Int. Surg., 52;405, 1969.

2. Archampong, E. Q.: Operative Treatment of Typhoid Perforation of the Bowel. Br. Med. J., 3:273, 1969.
3. Archampong, E. Q.: Typhoid Ileal Perforations: Why such Mortalities? Br. J. Surg., 63:317, 1976.
4. Boyd, W.: Pathology, Philadelphia, Lea and Febiger, 1970, pp. 326–331.
5. Conroy, J. V.: Acute Ileitis with Ulceration and Perforation due to Paratyphoid Fever—Report of Eighty-five cases. Milit. Med., 120:79, 1957.
6. Dawson, J. H.: Surgical Management of Typhoid Perforation of the Ileum. Am. Surg., 36:620, 1970.
7. Dickson, J. A. S. and Cole, G. J.: Perforation of the Terminal Ileum. Br. J. Surg., 51:893, 1964.
8. Huckstep, R. L.: Recent Advances in the Surgery of Typhoid Fever. Ann. R. Col. Surg. Eng., 26:207, 1960.
9. Huckstep, R. L.: Typhoid Fever and Other Salmonella Infections, Edinburgh, E. & S. Livingstone, Ltd., 1962, p. 190 ff.
10. Kaul, B. K.: Operative Management of Typhoid Perforation in Children. Int. Surg., 60:407, 1975.
11. Kim, J. P., Oh, S. K. and Jarrett, F.: Management of Ileal Perforation due to Typhoid Fever, Ann. Surg., 181:88, 1975.
12. Kissane, J. M.: Bacterial Diseases in Anderson, W. A. D. and Kissane, J. M. (ed.) Pathology, St. Louis, C. V. Mosby, 1977, p. 397 ff.
13. Mulligan, T. O.: The Treatment of Typhoid Perforation of the Ileum. J. R. Col. Surg. Edin., 17:364, 1972.
14. Olurin, E. O., Ajayi, O. O. and Bohrer, S. P.: Typhoid Perforations. J. R. Col. Surg. Edin., 17:353, 1972.
15. Prasad, P. B., Choudhury, D. K. and Prakash, O.: Typhoid Perforation Treated by Closure and Proximal side-to-side Ileotransverse Colostomy. J. Ind. Med. Assoc., 65:297, 1975.
16. Rowland, H. A. K.: The Complications of Typhoid Fever. J. Trop. Med. Hyg., 64:143, 1961.
17. Samantray, S. K., Johnson, S. C., and Chakrabarti, A. K.: Enteric Fever: An Analysis of 500 Cases. Practitioner, 218:400, 1977.
18. Spray, G., Ejazy, M. M. and Rahini, N.: 31 Cases of Ileal Perforation Due to Typhoid. Place of Temporary Ileostomy with Resection. J. Chir. (Paris), 106:341, 1973.
19. Tseng, H. C. and Feng, C. H.: Perforation of Typhoid Ulcer. Chinese Med. J., 67:531, 1949.
20. Welch, T. P. and Martin, N. C.: Surgical Treatment of Typhoid Perforation. Lancet, 1:1078, 1975.

Initial Treatment of Sigmoid Volvulous by Colonoscopy

JAMES R. STARLING, M.D.

The initial management of acute, nonstrangulated sigmoid volvulous is to attempt proctosigmoidoscopic, rectal tube, or barium enema reduction and evacuation. If unsuccessful emergency surgery is necessary. The flexible colonoscope offers an additional therapeutic modality to effectuate preoperative reduction of the twisted sigmoid colon if attempts with conventional methods fail. Three cases of acute sigmoid volvulous are presented which illustrate for the first time successful reduction of acute sigmoid volvulous by colonoscopy after failure of the usual methods of treatment. Instead of emergency surgery all of these patients had elective resection with primary colocolostomy. Patients with acute sigmoid volvulous refractile to reduction by conventional modalities should have an attempt at flexible colonoscopic reduction.

THE INITIAL THERAPY of nonstrangulated sigmoid volvulous is nonoperative reduction and decompression. The three nonoperative technics utilized are proctosigmoidoscopic, barium enema, or rectal tube reduction and decompression. Successful reduction of sigmoid volvulous following attempts at one or all of these conventional modalities have ranged from 70 to 90%; with complications in the range of 1–2%.[2,4,5,7,8] If nonoperative therapy is unsuccessful, an emergency surgical procedure is necessary. Emergency surgery for sigmoid volvulous carries a 38% to 50% mortality rate for resection,[2,8] or an unacceptably high incidence or recurrent volvulous with simple operative detorsion and fixation.[2,5,9] Most surgeons are wisely reluctant to attempt resection with primary anastomosis in patients with unprepared, distended, and edematous bowel.

The literature supports the concept that nearly all patients who are successfully decompressed nonoperatively should undergo elective sigmoid resection after proper bowel preparation and consideration of other medical problems frequently seen in these patients. Elective resection of the sigmoid colon with primary anastomosis reduces the operative mortality to an acceptable rate, eliminates the likelihood of recurrent volvulous after nonoperative or nondefinitive surgical procedures, and eliminates the need for staged operations.

From the Department of Surgery, Veterans Administration Hospital and University of Wisconsin Medical Center, Madison, Wisconsin

Recently, three patients with acute sigmoid volvulous were initially successfully treated by colonscopy after attempts at proctosigmoidoscopic, rectal tube, or barium enema reduction failed. In all patients the level of distal sigmoid obstruction was above 25 cm. Nonoperative detorsion and deflation were accomplished using the flexible colonoscope. All patients subsequently were prepared for elective resection with primary anastomosis.

Case Reports

Case 1. The patient is a 50-year-old white man admitted to the neurology service for evaluation of a chronic seizure disorder for which he was taking Dilantin® and phenobarbital. During the course of this admission the patient began to complain of constipation, diffuse colicky abdominal pain, and distension. At the time of surgical evaluation his vital signs were normal. His white blood cell count was 9.0 per mm,[3] hemoglobin 12.7 g/dl, and hematocrit 37.5%.

Survey radiographs of the abdomen showed mechanical obstruction of the large bowel consistent with a sigmoid volvulous.

A proctosigmoidoscopy examination was normal to 25 cm. A rectal tube could be passed only to 25–30 cm and did not relieve the obstruction. A barium enema was performed which intensified the patient's pain and revealed a bird's beak appearance of the sigmoid colon with only a minimal amount of contrast material passing through a narrowed segment of colon.

The flexible colonoscope was then inserted. At approximately 35–40 cm the region of sigmoid torsion was appreciated. Under direct vision with gentle air insufflation the area was open and the sigmoid underwent detorsion. Copious amounts of gas and loose stool were evacuated. The scope was then advanced under direct visualization through the redundant loop of sigmoid colon which extended into the right upper quadrant of the abdomen to a distance of 120 cm (Fig. 1). Gas and stool which had accumulated in the proximal sigmoid was evacuated. The colonic mucosa appeared viable. Twenty-four hours after colonoscope reduction the patient complained of slight abdominal pain and had a temperature of 39.5°. There was no elevation of his white blood cell count or peritonea signs. He was returned to the endoscopy unit where repea colonoscopy was performed to 120 cm without evidence of recurrer volvulous, strangulated bowel, or reaccumulation of gas or stool.

Eight days later the patient underwent elective sigmoid resecti of 31 cm of redundant bowel with primary anastomosis. He w

---

Reprint requests: James R. Starling, M.D., Department of Surgery, University of Wisconsin Medical Center, Madison, WI 53705.

Submitted for publication: January 2, 1979.

0003-4932/79/0700/0036 $00.70 © J. B. Lippincott Company

discharged nine days later and continues to be asymptomatic 15 months postoperatively.

Case 2. A 48-year-old white man was admitted to the hospital with the chief complaint of diffuse, colicky abdominal pain associated with constipation of several days duration. There was no history of nausea, vomiting, or fever. He had a previous admission to the University of Wisconsin Hospital 14 months prior to this hospitalization at which time a cecal volvulous was treated by cecopexy and tube cecostomy. His recovery from this surgery was uneventful.

Examination at this admission showed a patient with normal vital signs except for a pulse rate of 112 per min. His abdomen was enormously distended with faint, hypoactive bowel sounds. Tympany to percussion was present with mild diffuse tenderness to palpation. There was no rebound, point tenderness, or board-like rigidity. No stool was present in the rectum.

His admission white blood count was 12,500 per mm^3, hemoglobin 16.7 g/dl, and hematocrit 48.1%. Survey radiographs of the abdomen showed findings consistent with colonic obstruction secondary to a sigmoid volvulous.

Parenteral fluid therapy was begun and a nasogastric tube placed. The patient was taken to the endoscopy unit where a sigmoidoscope was passed to 25 cm. A rectal tube could not be passed beyond 35 cm. The flexible colonoscope was then inserted into the unprepared bowel which visualized the point of torsion at approximately 35 cm. With air insufflation and gentle pressure the twisted sigmoid colon underwent detorsion with immediate evacuation of gas and dark green liquid stool. This immediately relieved the abdominal distention. The scope was then advanced with care under direct vision to 60 cm and more residual gas and stool evacuated (Fig. 2). The bowel was massively distended and edematous, but the mucosa was viable. Diverticula were seen near the area of sigmoid torsion.

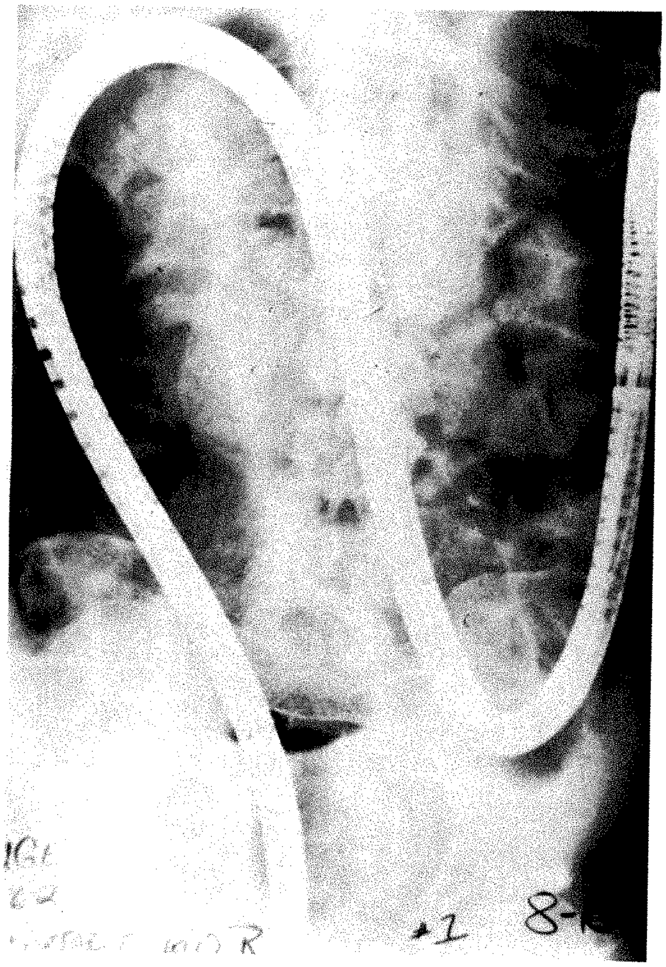


FIG. 1. Abdominal radiograph with colonoscope inserted through the twisted segment of sigmoid volvulous.

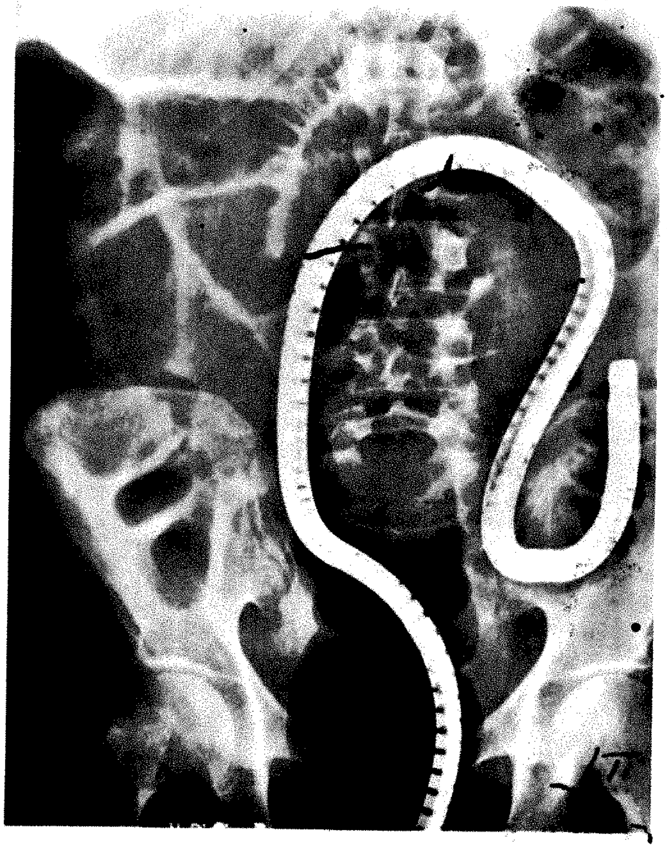


FIG. 2. Abdominal radiograph taken immediately after detorsion of the sigmoid volvulous. Residual gas is still present in the redundant sigmoid loop.

The patient was subsequently placed on a mechanical and antibiotic bowel prep and underwent elective resection of 28 cm of sigmoid colon with primary anastomosis. He was discharged from the hospital in eight days and continued to be asymptomatic 12 months postoperatively.

Case 3. The patient is a 62-year-old white man with a history of multiple sclerosis. For three months prior to admission the patient reported intermittent bouts of constipation. The patient was admitted to the hospital because of a distended, tympanitic abdomen concurrent with no bowel movement for three days.

At the time of admission, the patient's vital signs were normal. His abdomen was markedly distended but without tenderness. There was no stool in the rectum. His white blood cell count, hematogram, and screening electrolytes were within normal limits. Survey radiographs of the abdomen demonstrated obstruction of the large bowel consistent with sigmoid volvulous.

Emergency proctosigmoidoscopy to 25 cm was successful in evacuating a small amount of gas and loose stool. A rectal tube was passed to 60 cm and fixed into position. Abdominal x-rays at this time revealed partial improvement in the degree of colonic obstruction. During the following 12 hours despite the indwelling rectal tube and nasogastric intubation, the patient became massively distended with x-rays showing sigmoid volvulous and colonic ob-

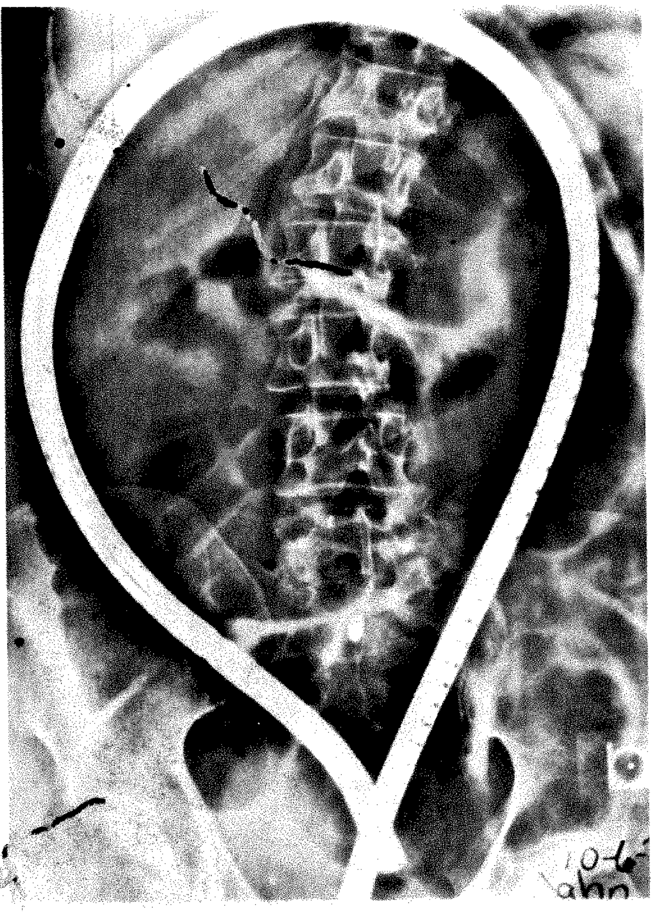


FIG. 3. Abdominal radiograph showing the tip of the colonoscope entering the twisted segment of sigmoid colon.

struction. Proctosigmoidoscopy did not evacuate gas and stool as had been the initial result. Consequently, the flexible colonoscope was passed which showed a sigmoid torsion which was reduced with gentle pressure and air insufflation. The scope was then advanced through the redundant loop of sigmoid colon to a distance of 120 cm with evacuation of copious amounts of gas and liquid stool, until the distended bowel became flaccid (Figs. 3 and 4). No evidence of strangulation was seen.

No recurrent volvulous occurred and the patient underwent elective resection of 60 cm of redundant sigmoid colon with primary anastomosis seven days after admission. His postoperative course has been uneventful.

Discussion

Ghazi, Shinya, and Wolff[5] have reported on a single patient in which colonoscopy was successful in reduction of chronic sigmoid volvulous. However, in their patient sigmoidoscopy had been successful on numerous occasions in the past to reduce the recurrent sigmoid volvulous. In the three patients discussed above emergency proctosigmoidoscopy, and rectal tube decompression were unsuccessful in reducing the volvulous. A barium enema was unsuccessful in one patient. Despite the lack of evidence for strangulation all three of these patients would have required emergency celiotomy. Flexible colonoscopy successfully reduced the twisted sigmoid colon and allowed proximal evacuation. Primary resection with end-to-end colocolostomy was done electively without complication after bowel preparation and restoration of other systemic disturbances.

When conventional methods of nonoperative treatment cannot reach the site of sigmoid volvulous or effect decompression, an emergency surgical procedure is necessary with resultant high morbidity and mortality. The flexible colonoscope makes it possible to reach the region of volvulous occurring proximal to 25 cm. In addition, the colonic mucosa can be evaluated by direct vision in the proximal sigmoid colon. Therefore, more effective and thorough evacuation of gas and stool can be obtained.

It is known that adynamic ileus and volvulous can coexist.[3] The flexible colonoscope allows evacuation and evaluation of the atonic, edematous, friable proximal bowel. The ability to evacuate the bowel beyond the reach of the proctosigmoidoscope and/or rectal tube may allow a faster return of effective

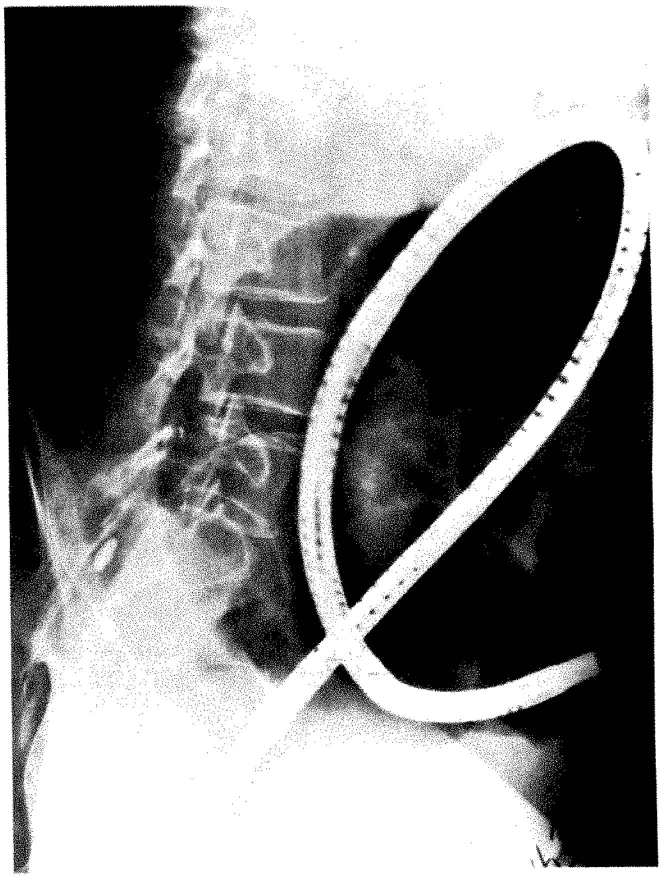


FIG. 4. Lateral abdominal radiograph showing the tip of the colonoscope through the area of twisted segment of sigmoid colon after detorsion.

colonic peristalsis and reduce the possibility of recurrent volvulous due to the pressure of retained gas and stool.

If proctosigmoidoscopy or colonoscopy reveals a bloody discharge or evidence of strangulation the procedure should be terminated and emergency celiotomy performed. Patients with physical or systemic signs of colonic strangulation should not be considered for nonoperative reduction of the volvulous by any method.

The possible role of the colonoscope for the initial treatment of colonic volvulous other than sigmoid is still uncertain. Although one patient with cecal volvulous has been reported where the volvulous was successfully reduced using the colonoscope and emergency surgery avoided,[1] an attempt at colonoscopic reduction of a cecal volvulous by this author was unsuccessful.

References

1. Anderson, M. J., Okike, N. and Spencer, R. J.: The Colonoscope in Cecal Volvulous. Dis. Colon Rectum, 21:71–74, 1978.
2. Arnold, G. J. and Nance, F. C.: Volvulous of the Sigmoid Colon. Ann. Surg., 177:527, 1973.
3. Botsford, T. W., Healey, S. J. and Veith, F.: Volvulous of the Colon. Am. J. Surg., 114:900, 1967.
4. Bruusgaard, C.: Volvulous of the Sigmoid Colon and its Treatment. Surgery, 22:466, 1947.
5. Drapanas, T. and Stewart, J. D.: Acute Sigmoid Volvulous: Concepts in Surgical Treatment. Am. J. Surg., 101:70, 1961.
6. Ghazi, Ali, Shinya, Hiromi and Wolff, W. I.: Treatment of Volvulous of the Colon by Colonoscopy. Ann. Surg., 183: 263, 1976.
7. Nay, H. R., West, J. P.: Treatment of Volvulous of the Sigmoid Colon and Cecum. Arch. Surg., 94:11, 1967.
8. Shepherd, J. J.: Treatment of Volvulous of Sigmoid Colon: A Review of 425 Cases. Br. Med. J. 1:280, 1968.
9. Sutcliffe, M. M. L.: Volvulous of the sigmoid Colon. Br. J. Surg. 55:903, 1968.

Megacolon in the Elderly

Ischemic or Inflammatory?

IRVING B. MARGOLIS, M.D., RICHARD S. FARO, M.D., EARL M. HOWELLS, M.D., CLAUDE H. ORGAN, JR., M.D.

Ischemic colitis has been previously described in three forms: transient, strictured, and gangrenous. A fourth form of presentation in the elderly is characterized by signs of an acute abdomen, massive colonic dilatation, and systemic toxicity. Bloody diarrhea may be seen prior to the onset of dilatation. Ischemia should be considered as an etiologic factor in "colitis" in the elderly patient with segmental dilatation particularly if it follows a "low flow state." The rectum is usually uninvolved. Barium enema may confirm segmental involvement and later demonstrate stricture. Three patients with ischemic megacolon are presented. The diagnosis was suspected preoperatively in only one. In contrast to ulcerative colitis, these patients show a more abrupt onset and run a fulminant course. In patients who recover, there is lower relapse rate than young patients with ulcerative colitis. When resection is indicated, all attempts should be made to spare the rectum. Loop ileostomy and decompressive colostomy offer an excellent temporizing measure to assist the patient through the acute phase of the illness.

"TOXIC MEGACOLON" IS A CONDITION most clinicians associate with fulminant ulcerative colitis in the young adult. When such presentations occur in the elderly numerous diagnostic and therapeutic problems are posed.

Colonic dilatation mimicking "toxic megacolon," secondary to ischemic colitis, was first described by Rosato in two patients who had full thickness ischemic necrosis of the transverse colon.[9] Kaminski's study suggests that the presence of dilatation of the colon on abdominal films during the course of ischemic colitis indicates a full thickness colon infarction.[5]

The purpose of this paper is to present three patients we have encountered and managed with documented ischemic colitis who developed the radiographic features of "toxic megacolon" without full thickness necrosis of the dilated segment of colon, and to identify the problems in diagnosis and treatment of this entity.

From the Department of Surgery, Creighton University School of Medicine, Omaha, Nebraska

Case Reports

Case 1. This 69-year-old man presented with abdominal pain, distention, and melena of seven day's duration. The patient experienced similar complaints five months previously and evaluation at another hospital on two occasions revealed probable ulcerative colitis. Proctocolectomy had been advised, but the patient refused.

Significant findings on physical examination included an oral temperature of 36.1°, pulse rate of 130, abdominal distention, and a palpable mass extending from left upper to lower quadrants. Black liquid stool was noted on rectal examination. Abdominal films (Fig. 1) revealed marked dilatation of the transverse colon. Following 24 hours of intravenous hydration and observation, no improvement in the distention was observed. Operative intervention was mandated and a loop ileostomy and decompressive right colostomy were performed. Transoperatively, the patient sustained a silent subendocardial infarction from which he recovered satisfactorily postoperatively. A biopsy of the transverse colon obtained at the time of operative decompression revealed a segment of colon showing marked edema. Proctoscopic examination one month postoperatively revealed normal rectal mucosa to the 13 cm level. A biopsy at 8 cm showed chronic inflammation but, on retrospective review, was within normal limits. Barium enema revealed marked stricture of the descending and transverse colons (Fig. 2). Visceral angiography revealed minimal stenosis of the celiac trunk and complete occlusion of the inferior mesenteric artery.

Three months postoperatively a subtotal colectomy with end ileostomy was performed. Ileoproctostomy was not performed because of possible rectal involvement. Pathologic examination of the resected specimen revealed mucosal ulceration and stricture of the descending colon. Further proximal sections showed a progressive change toward normal colonic mucosa. The patient has remained asymptomatic for three years following the second procedure. The final diagnosis was ischemic colitis.

Comment

The limited initial operative procedure in this critically ill patient permitted him to recover from the acute phase of the illness. Intestinal continuity was not restored because of the possibility of rectal involvement. Had the ischemic etiology of the problem in this patient

---

Reprint requests: Irving B. Margolis, M.D., Creighton University School of Medicine, Department of Surgery, 601 North 30th Street, Omaha, Nebraska 68131.

Submitted for Publication: December 15, 1978.

0003-4932/79/0700/0040 $00.75 © J. B. Lippincott Company

been recognized at the time, coloproctostomy using the ascending colon could have been performed.

Case 2. This 55-year-old man, sustained a cardiac arrest at home and responded to cardiopulmonary resuscitation. Successful cardioversion for ventricular fibrillation was carried out on admission to the emergency room. He was transferred to ICU in a comatose state with flail chest secondary to resuscitation. A tracheostomy was performed to stabilize the flail chest on the second hospital day.

Over the next two weeks he developed intermittent sepsis (thought to be pulmonary in origin) and abdominal distention. Abdominal films obtained early in the course revealed excessive gas in the small and large bowel which was compatible with paralytic ileus. His sensorium slowly cleared, but the abdominal distention persisted. Barium enema and proctosigmoidoscopy were within normal limits. By the fourteenth hospital day, abdominal films revealed distention of the transverse colon to a diameter of 8 cm. Over the next two weeks, the colonic diameter progressed to 15 cm (Fig. 3). On the thirty-second hospital day, a pneumoperitoneum was noted on a routine chest x-ray.

Exploratory laparotomy revealed moderate fecal contamination, a 0.5 cm perforation of the descending limb of the splenic flexure, and massive distention of the transverse and ascending colons. The ascending and transverse colons were resected and ileostomy and mucous fistula of the descending colon established. The peritonitis slowly improved and the patient was discharged on the eightieth hospital day. The initial pathology report on the resected colon was "perforated ulcerative colitis (toxic megacolon) of the ascending and transverse colon" (Fig. 4a).

One year later, the patient was admitted for examination of the distal colon. Barium enema and colonoscopy with biopsy of the remaining colon were within normal limits. Gastrointestinal continuity was re-established on this admission by ileosigmoid anastomosis. Histologic examination of the resected descending colon was within normal limits (Fig. 4b) and the pathology diagnosis was revised to that of ischemic colitis. He has remained asymptomatic for three and one-half years.

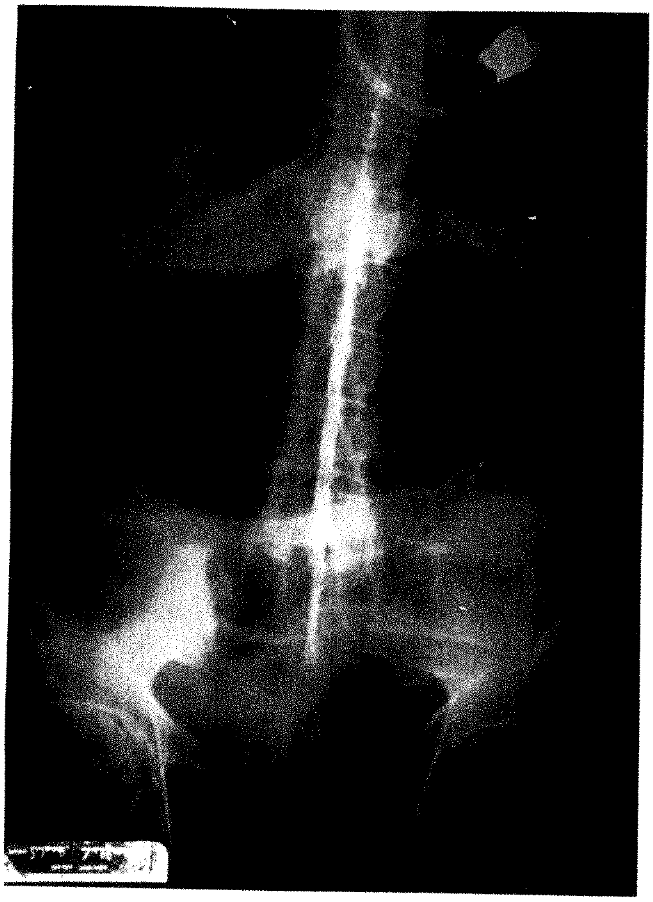


FIG. 1. Case 1. Plain abdominal film demonstrating massive dilatation of the transverse colons.

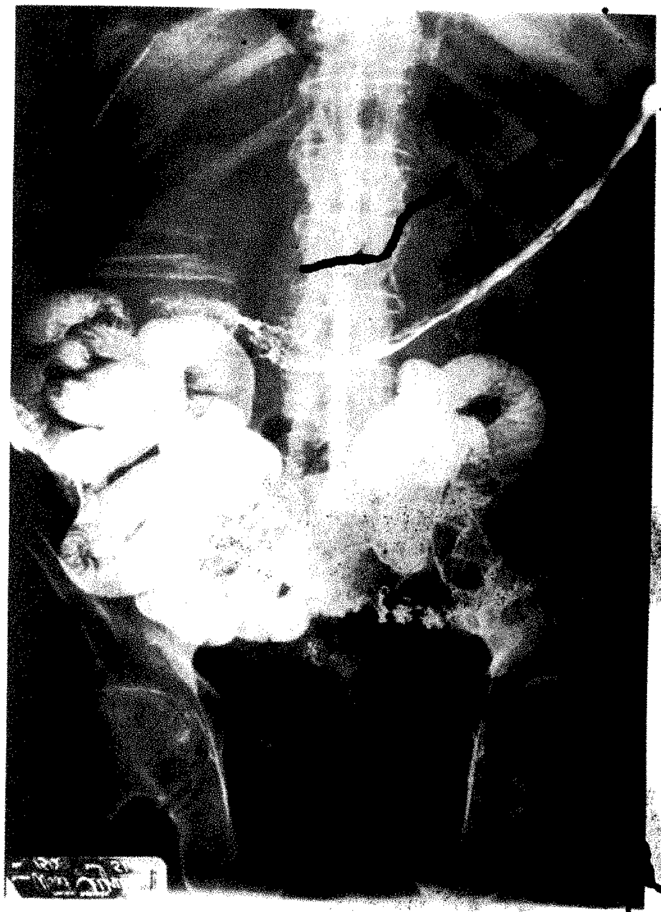


FIG. 2. Case 1. Barium enema one month after decompression revealing marked stricture of the descending and transverse colons.

Comment

In retrospect, had the ischemic etiology of the problem been identified, there would have been no need to resect the descending colon at the second operative procedure.

Case 3. This 54-year-old man, presented with left lower quadrant abdominal pain of 24-hours duration. He vomited one time following the onset of pain and subsequently passed no flatus or stool. Positive physical findings included abdominal distention, left lower quadrant tenderness, and hypoactive bowel sounds. The white blood cell count was 30,500. Plain films of the abdomen revealed an excessive amount of gas in the transverse colon with no small bowel gas visualized.

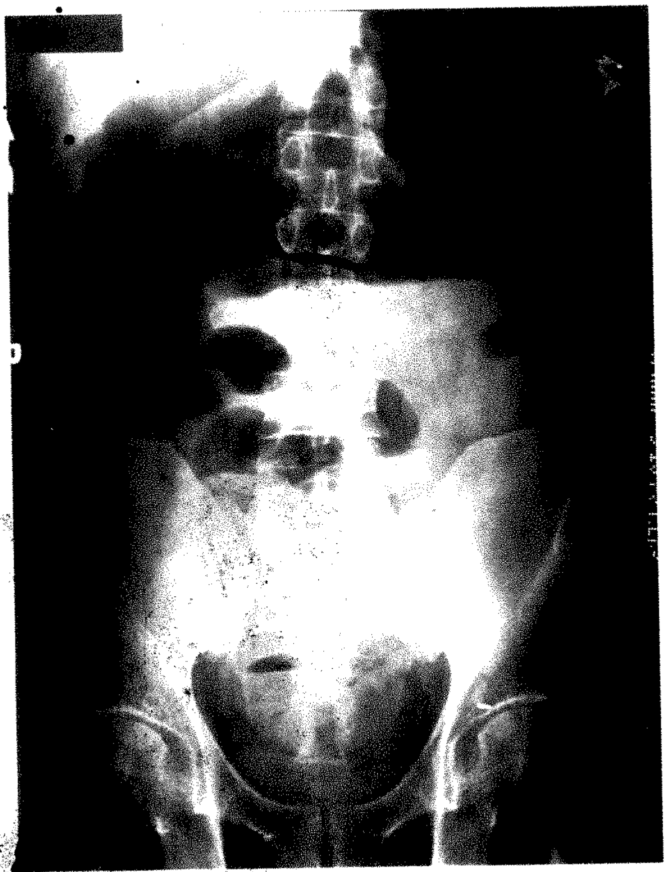


FIG. 3. Case 2. Plain abdominal film demonstrating massive dilatation of the transverse colon.

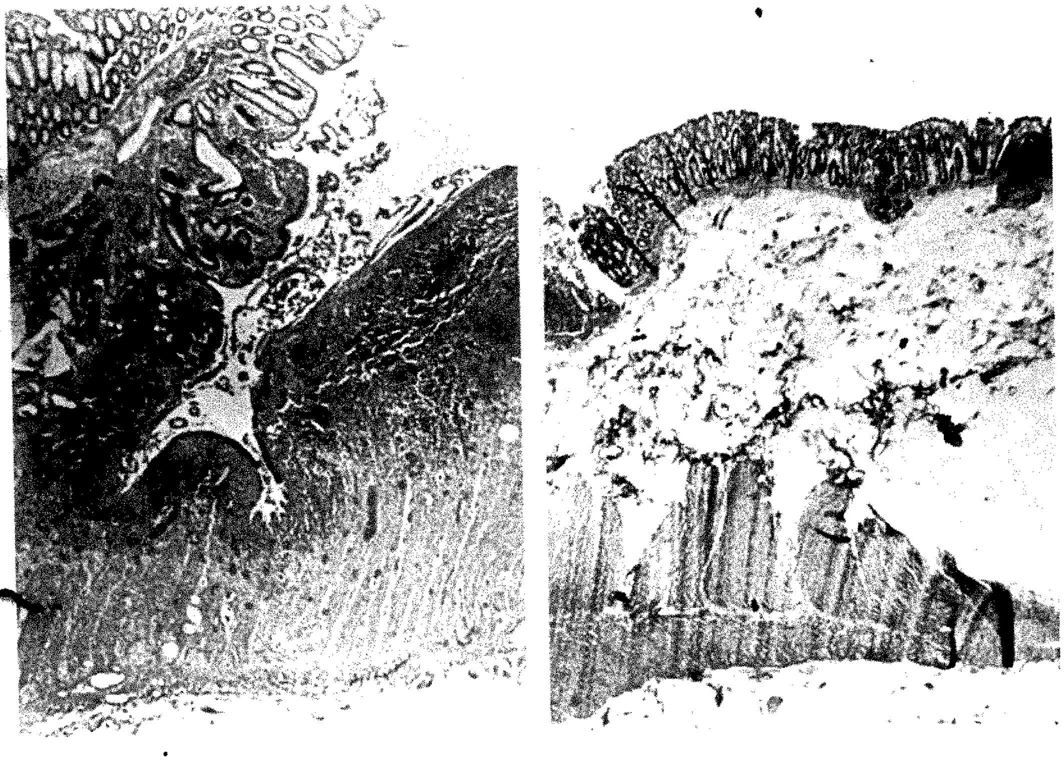
Because of an initial diagnosis of acute sigmoid diverticulitis, treatment was initiated with nasogastric suction, intravenous fluids, and parenteral antibiotics with slow improvement over the next ten days. Barium enema revealed a loss of mucosal pattern in the sigmoid and descending colon and a long fistula parallel and adjacent to the descending colon. The radiographic impression was that of granulomatous colitis. Proctosigmoidoscopy was normal up to 13 cm. Above this point, the bowel mucosa appeared hemorrhagic and ulcerated. A biopsy of the abnormal areas revealed no recognizable colon mucosa with only fragments of mesocolon with fat necrosis and was interpreted as inflammation and necrosis of mesocolon compatible with ulcerative colitis.

These radiographic findings and tissue reports supported the diagnosis of inflammatory bowel disease with fistula formation. Eight weeks following admission, total proctocolectomy and ileostomy were performed. At operation normal ascending and transverse colons with a long stricture of the descending colon were found. Histologically, the segment of descending and proximal sigmoid colon revealed replacement of mucosa and submucosa by granulation tissue. The small arteries of the mesentery and muscularis were completely occluded (Fig. 5a). The rectum and distal sigmoid were within normal limits (Fig. 5b). The final diagnosis was ischemic colitis of the descending and sigmoid colon.

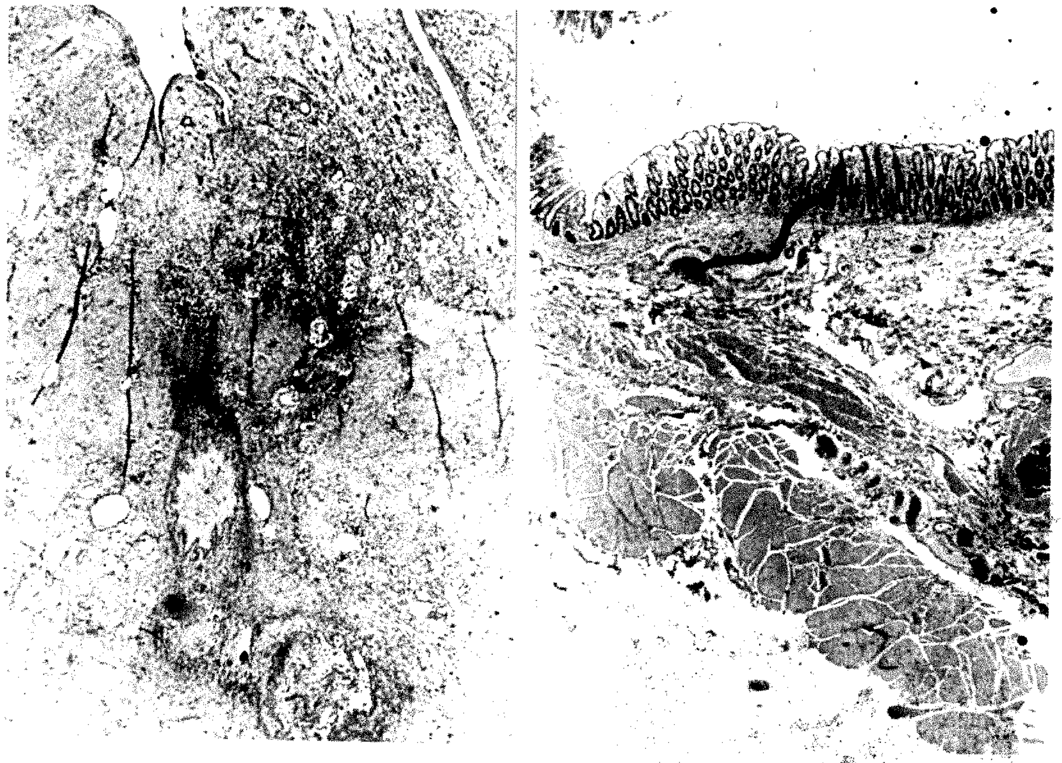
The patient has had multiple admissions for problems related to peptic ulcer and peripheral vascular disease over the past six years but no further intestinal difficulties.

Comment

Had the ischemic nature of the problem in this patient been recognized preoperatively, resection could have been limited to the involved portion of the sigmoid and descending colon with restoration of intestinal continuity by transverse coloproctostomy.



FIGS. 4a and b. (*a, left*) Case 2. Resected transverse colon revealing normal mucosa adjacent to ulceration, mimicking "pseudopolyp." (*b, right*) Sigmoid colon resected one year later is normal.



FIGS. 5a and b. (*a, left*) Case 3. Descending colon revealing replacement of mucosa by granulation tissue, submucosal fibrosis, cholesterol embolus, and thrombosis of submucosal vessles. (*b, right*) Normal appearing rectum.

Discussion

Most patients with ischemic colitis can be classified according to Marston's criteria: transient, ischemic stricture, or gangrenous.[7] Our three patients appear to fit into the ischemic stricture category. Their clinical courses were similar to Case 5 in Marston's series, an example of ischemic stricture formation. All of our patients had acute abdominal findings and systemic toxicity and one had a free perforation of the colon. Plain films of the abdomen suggested "toxic megacolon" in all three cases.

All three of our patients were over 50 years of age with pre-existing arteriosclerotic vascular disease. One patient had hypotension due to a cardiac arrhythmia. All had a prodrome of abdominal symptoms lasting at least three weeks prior to definitive therapy. The colonic segment involved with severe ischemic colitis was the same—the descending colon. None of our patients had rectal involvement grossly or by biopsy. Barium enema performed in all patients did not demonstrate "thumbprinting," the diagnostic hallmark of ischemic colitis.

The basic cause of ischemic megacolon appears to be functional obstruction distal to the splenic flexure with secondary dilatation of the transverse colon. Paralytic ileus secondary to deep ulceration in the transverse colon may have contributed to the development of megacolon. The length of the strictured segment varied from 2 cm (Case 2) to 50 cm (Case 3). Involvement of the transverse colon varied from severe (Case 2) to minimal (Case 3) ulceration.

The elderly patient presenting with acute colonic distention on abdominal films poses subtle problems. The differential diagnosis should include ulcerative colitis, granulomatous colitis, amebic colitis, carcinoma of the colon, paralytic colonic ileus, and ischemic megacolon. Evans and Acheson[3] have demonstrated a second peak in the incidence rate of ulcerative colitis at age 60 and others[1,2,8] have sensitized the clinician to the occurrence of ulcerative colitis in the elderly. The bimodal shape of the age incidence curve, however, suggests a different disease entity in the elderly with presumed ulcerative colitis. Retrospective studies[10] reveal the elderly respond differently with presumed ulcerative colitis. A more abrupt onset, fewer systemic complications, and lower recurrence rate following resolution are features of the disease in the elderly. Ulcerative colitis is thought to be an autoimmune disease and alterations in cell-mediated immunity and immunoglobulin in the elderly may partially explain the clinical differences.[4] Another explanation, however, may be that a significant number of these patients are suffering from ischemic colitis.

Evaluation of the elderly patient with "toxic megacolon" should include good quality plain abdominal films and proctosigmoidoscopy with biopsy. Spot films of the left upper quadrant may be helpful in revealing the diameter of the splenic flexure. The findings of normal-appearing rectal mucosa excludes ulcerative colitis. Although ischemic ulceration of the rectum can occur, it is unusual.[6]

Better histologic criteria are now available for interpretation of endoscopic biopsy in ischemic colitis.[12] Our pathologists originally were quite liberal with the diagnosis of ulcerative colitis in these patients. Careful histologic examination is the most important diagnostic procedure in this disease and should yield the correct diagnosis.

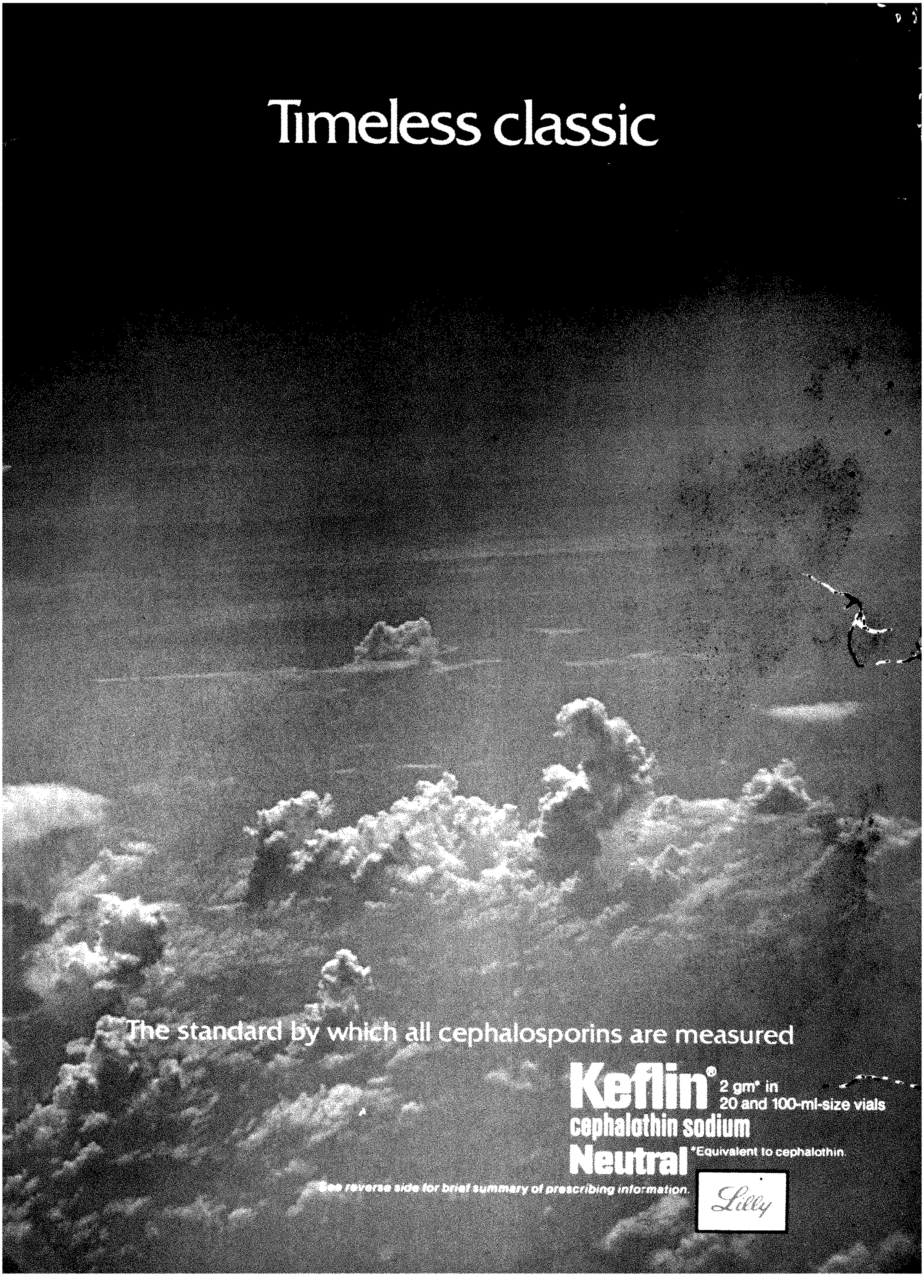
The role of barium enema examination in diagnosis of this condition is difficult to define. Barium examination should be avoided in the acute phase of this disease for fear of perforation of the acutely distended bowel and because its possible etiologic role in the toxic megacolon of ulcerative colitis. Once the acute process has resolved, contrast studies are quite valuable in delineating strictured segments.

Arteriography plays a minor role in the diagnosis of this problem. Many patients with documented ischemic colitis with normal visceral angiography have been reported and the changes seen in some patients are not specific. Magnification techniques with focus on the smaller colonic vessels may be useful in the future.

The treatment of ischemic megacolon is primarily surgical. Rosato[9] and Kaminski[5] have demonstrated the high incidence of gangrene in megacolon of ischemic colitis. Gangrenous segments should be resected with exteriorization of the bowel. If full thickness necrosis is not present, a number of options exist. Excision of the rectum should be avoided. Resection of dilated transverse colon with or without anastomosis is appealing, but perforation during resection may occur. We recommend ileostomy and decompressive colostomy for toxic megacolon in ulcerative colitis. After a two month recovery interval, endoscopy and barium enema can be performed. At this time, severely ischemic areas will have undergone stricture formation. Interval colectomy with ileosigmoid or ileorectal anastomosis may then be performed restoring gastrointestinal continuity.

References

1. Diethelm, A. G., Nickle, W. F., Jr. and Wantz, G. E.: Ulcerative Colotis in the Elderly Patient. Surg. Gynecol. Obstet., 126: 1223, 1968.
2. Earle, E. and Rowe, R. J.: Ulcerative Disease of the Large Intestine in Patients More than 50 Years Old. Dis. Colon. Rectum., 15(1):33, 1972.
3. Evans, J. G. and Acheson, E. D.: An Epidemiological Study of Ulcerative Colitis and Regional Enteritis in the Oxford Area. Gut, 6:311, 1965.
4. Gebbers, J. O. and Otto, H. F.: Ulcerative Colitis in the Elderly. Lancet, 2:714, 1975.
5. Kaminski, D. L., Keltner, R. M. and Willman, V. L.: Ischemic Colitis. Arch. Surg. 106:558, 1973.
6. Kilpatrick, A. M., Farman, J., Yesner, R., et al.: Ischemic Proctitis. JAMA 205(2):64, 1968.
7. Marston, A., Pheils, M. T., Thomas, M. L., et al.: Ischemic Colitis. Gut, 7:1, 1966.
8. Rogers, B. H. G., Clark, L. M. and Kirsner, J. B.: The Epidemiologic and Demographic Characteristics of Inflammatory Bowel Disease: An Analysis of a Computerized File of 1400 Patients. J. Chronic Dis., 24:743, 1971.
9. Rosato, E. F., Rosato, F. E., Scott, J., et al: Ischemic Dilatation of the Colon. Am. J. Dig. Dis., New Series 14:922, 1969.
10. Toghill, P. J. and Benton, P.: Ulcerative Colitis in Elderly Patients. Geront. Clin., 15:65, 1973.
11. Turnbull, R. B., Jr., Hawk, W. A. and Weakley, F. L.: The Surgical Treatment of Toxic Megacolon. Ileostomy and Colostomy to Prepare Patients for Colectomy. Am. J. Surg. 122: 325, 1971.
12. Whitehead, R.: Mucosal Biopsy of the Gastrointestinal Tract. Philadelphia, W. B. Saunders, 1973, pp. 139–166.


Timeless classic
The standard by which all cephalosporins are measured
Keflin® 2 gm* in 20 and 100-ml-size vials
cephalothin sodium
Neutral
*Equivalent to cephalothin.
See reverse side for brief summary of prescribing information.
Lilly

Keflin®
cephalothin sodium
Neutral

Brief Summary.
Consult the package literature for prescribing information.

Indications: Keflin, Neutral, for Injection, is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below.

Respiratory tract infections caused by *Streptococcus pneumoniae*, staphylococci (penicillinase and non-penicillinase-producing), group A beta-hemolytic streptococci, *Klebsiella*, and *Haemophilus influenzae*

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and non-penicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*

Genitourinary tract infections caused by *E. coli*, *P. mirabilis*, and *Klebsiella*

Septicemia, including endocarditis, caused by *S. pneumoniae*, staphylococci (penicillinase and non-penicillinase-producing), group A beta-hemolytic streptococci, *S. viridans*, *E. coli*, *P. mirabilis*, and *Klebsiella*

Gastrointestinal infections caused by *Salmonella* and *Shigella* species

Meningitis caused by *S. pneumoniae*, group A beta-hemolytic streptococci, and staphylococci (penicillinase and non-penicillinase-producing)

NOTE: Inasmuch as only low levels of Keflin are found in the cerebrospinal fluid, the drug is not reliable in the treatment of meningitis and cannot be recommended for that purpose. Keflin has, however, proved to be effective in a number of cases of meningitis and may be considered for unusual circumstances in which other, more reliably effective antibiotics cannot be used.

Bone and joint infections caused by staphylococci (penicillinase and non-penicillinase-producing)

NOTE: If the susceptibility tests show that the causative organism is resistant to Keflin, other appropriate antibiotic therapy should be instituted.

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy—Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported. [100678]

Lilly

Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

801025

Gangrene and Severe Ischemia of the Lower Extremities

Edited by JOHN J. BERGAN, M.D., and
JAMES S. T. YAO, M.D., Ph.D.

Gangrene can afflict those least able to bear the economic, psychological, and physical trauma of amputation. Focusing on this problem, the eminent contributors to this volume examine the factors which can lead to successful prevention of gangrene as well as treatment. The book contains the proceedings of the Symposium on Gangrene and Severe Ischemia of the Lower Extremities, held at Northwestern University in Chicago, December, 1978. Highlights of the book include a discussion of the relationship of smoking to biochemical changes in the blood; a report by a well-known authority on the use of ultrasound in evaluation of patients who have needed amputation; presentation of a series of fifteen patients with confirmed Buerger's syndrome; useful information on direct revascularization; and a major philosophical statement on amputation as opposed to direct arterial reconstruction.

SECTION HEADINGS: Pathophysiology. Patient Evaluation When Gangrene Is Present. Nonatherosclerotic Ischemia. Reconstruction of Proximal Arteries. (Aorto-Iliac) In Patients With Severe Ischemia. Peri-Operative Assessment of Patient Revascularization.

1978, 488 pp., illus., $29.75 ISBN: 0-8089-1158-9

Send payment with order and save postage and handling charge. *Prices are subject to change without notice.*

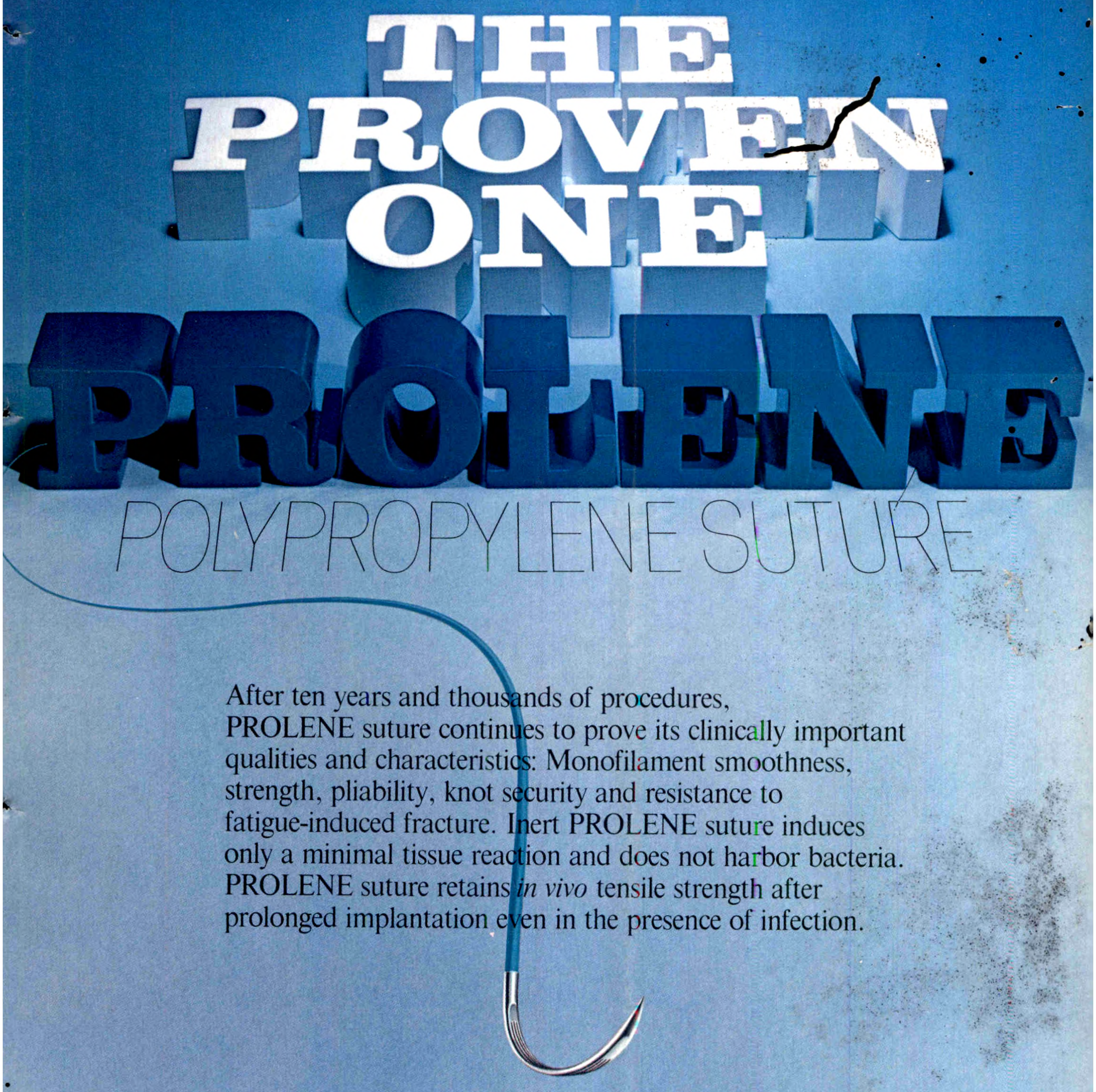
Grune & Stratton
A Subsidary of Harcourt Brace Jovanovich, Publishers
111 FIFTH AVENUE, NEW YORK, N.Y. 10003
24-28 OVAL ROAD, LONDON NW1 7DX

CHANGE OF ADDRESS

Change of Address: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the *Journal.*

Send Change of Address cards to:

ANNALS OF SURGERY
c/o Fulfillment Manager
East Washington Square
Philadelphia, Penna. 19105



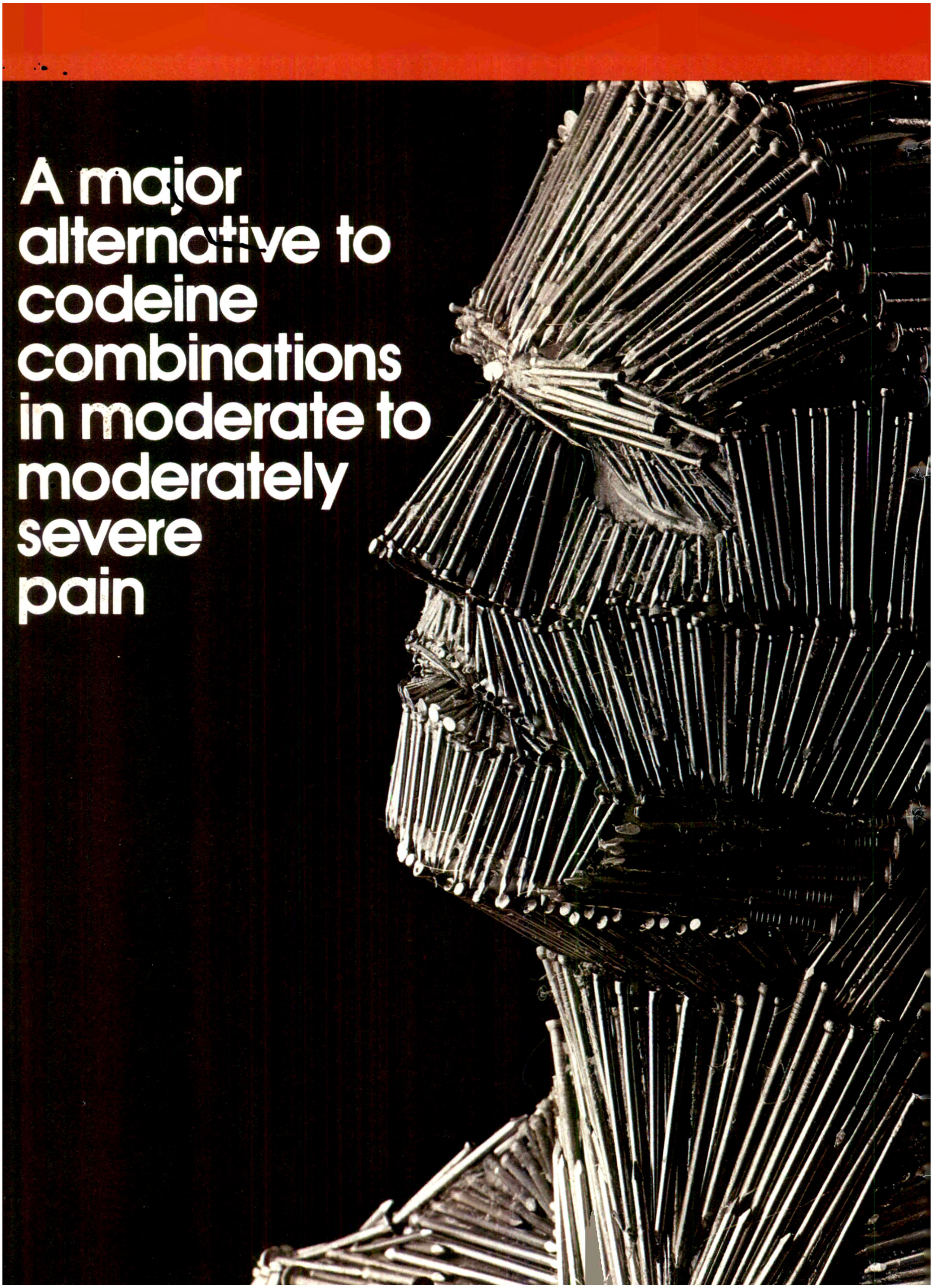
After ten years and thousands of procedures, PROLENE suture continues to prove its clinically important qualities and characteristics: Monofilament smoothness, strength, pliability, knot security and resistance to fatigue-induced fracture. Inert PROLENE suture induces only a minimal tissue reaction and does not harbor bacteria. PROLENE suture retains *in vivo* tensile strength after prolonged implantation even in the presence of infection.

ETHICON

INDICATIONS — PROLENE Polypropylene Suture, U.S.P. may be used wherever Nonabsorbable Surgical Suture, U.S.P. is recommended. Due to its relative biological inertness, it is recommended for use where the least possible suture reaction is desired. As a true monofilament, PROLENE Polypropylene Suture, U.S.P. resists involvement in infection and has been successfully employed in contaminated and infected wounds to eliminate or minimize later sinus formation and suture extrusion. Because of its lack of adherence to tissue, PROLENE Polypropylene Suture, U.S.P., is efficacious as a pull-out suture. **CONTRAINDICATIONS** — There are no known contraindications. **WARNINGS** — Unused PROLENE Polypropylene Sutures which have been removed from their package may be resterilized no more than three times by the standard steam autoclaving method (250°F for 30 minutes) without loss of strength. Unopened suture packages should not be resterilized by steam autoclave. **PRECAUTIONS** — As with other synthetic sutures, knot security requires the standard surgical technic of flat and square ties, with additional throws if indicated by surgical circumstance and the experience of the operator. **ADVERSE REACTIONS** — Transitory local inflammatory reactions have been reported. **SUPPLIED** — Available in U.S.P. sizes, with and without needles, 10/0 thru 2 for pigmented sutures; 7/0 thru 2 for clear.

*Trademark

© ETHICON, INC. 1979


A major alternative to codeine combinations in moderate to moderately severe pain

vicodin® CIII

hydrocodone bitartrate 5 mg. with acetaminophen 500 mg.

A unique narcotic analgesic formula with hydrocodone– a semi-synthetic analogue of codeine

combined with 500 mg. acetaminophen

Individual patient rating of treatment acceptability of VICODIN,® Tylenol® with Codeine No. 3, and placebo by 90 post-partum patients.

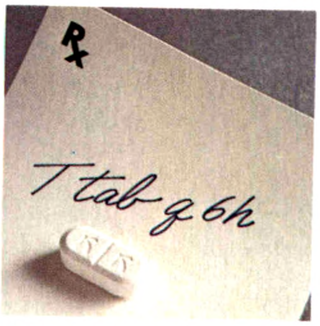
In a controlled double-blind study, 3 groups of 30 women with moderate episiotomy pain were treated with VICODIN,® Tylenol® with Codeine No. 3 or placebo[1]

	VICODIN®	Tylenol® with Codeine No. 3	Placebo
VERY GOOD	73% 22 of 30 patients	50% 15 of 30 patients	33% 10 of 30 patients
FAIR/ POOR	27% 8 of 30 patients	50% 15 of 30 patients	67% 20 of 30 patients

---

[1] Hopkinson, J. III: Vicodin. A new analgesic: Clinical evaluation of efficacy and safety of repeated doses. Curr. Ther. Res. 24(6):633-645, 1978.

DOSAGE CAN BE TITRATED TO MATCH THE SEVERITY OF PAIN



The usual adult dose is one tablet every 6 hours as needed for pain. In cases of more severe pain, two tablets every 6 hours or one tablet more frequently than every 6 hours may be required. VICODIN® is given orally. VICODIN Tablets are scored and can be easily divided for greater dosage flexibility.

Convenient telephone prescribing and ℞ refills.

Telephone prescribing is permissible in most states. Up to 5 refills in 6 months where state law permits.

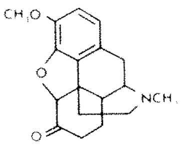
Please see next page for prescribing information

vicodin® CIII

hydrocodone bitartrate 5 mg. with acetaminophen 500 mg.

Description: Each tablet of VICODIN contains
Hydrocodone Bitartrate 5 mg.
Warning: May be habit forming.
Acetaminophen (APAP) 500 mg.
Acetaminophen occurs as a white, odorless crystalline powder, possessing a slightly bitter taste.

The hydrocodone component is dihydrocodeinone, a white, odorless crystalline powder which is derived from the opium alkaloid, thebaine, and may be represented by the following structural formula.



Actions: The principal analgesic ingredient, hydrocodone, is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine; most of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the hydrocodone in this drug are analgesia and sedation.

Hydrocodone is similar to codeine and methadone in that it retains at least one half of its analgesic activity when administered orally.

This drug also contains the non-narcotic antipyretic-analgesic acetaminophen.

Indications: For the relief of moderate to moderately severe pain.

Contraindications: Hypersensitivity to hydrocodone or acetaminophen.

Warnings: Drug Dependence: Hydrocodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, VICODIN (hydrocodone bitartrate with acetaminophen) is subject to the Federal Controlled Substances Act.

Usage in Ambulatory Patients: Hydrocodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Interaction with other central nervous system depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with hydrocodone and acetaminophen may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, VICODIN should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children: VICODIN should not be administered to children.

Precautions: Head injury and increased intracranial pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of VICODIN or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients: VICODIN should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease and prostatic hypertrophy or urethral stricture.

Adverse Reactions: The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

Dosage and Administration: The usual adult dose is one tablet every 6 hours as needed for pain. In cases of more severe pain, two tablets every 6 hours or one tablet more frequently than every 6 hours may be required. VICODIN is given orally.

Drug Interactions: The CNS depressant effects of this drug may be additive with that of other CNS depressants. See **Warnings.**

Management of Overdosage: Signs and Symptoms: Serious overdose with VICODIN (hydrocodone bitartrate with acetaminophen) is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of this drug may, in addition, result in acute hepatic toxicity.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including hydrocodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressor and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug. Acetaminophen in massive overdosage may cause hepatotoxicity in some patients. Clinical and laboratory evidence of hepatotoxicity may be delayed for up to one week. Close clinical monitoring and serial hepatic enzyme determinations are therefore recommended.

Treatment of acute acetaminophen overdosage is purely symptomatic.

How Supplied: Bottles of 100 white, bisected, flat capsule-shaped tablets with a double K logo.

Knoll Pharmaceutical Company, Whippany, New Jersey 07981
Member Company, Certified Medical Representatives Institute, Inc.

5629

What cancer can't kill:

HOPE. LOVE. COMPASSION. DIGNITY. TENDERNESS. UNDERSTANDING.

Because now there's a book of sound advice for everyone whose loved one has cancer.

How do you cope with cancer when someone you care for is the victim? How can you deal with the anger, fear and anxiety? Until now, the answer was a vague one. Today, however, there is a book—by an expert—that is a straightforward, wise, human discussion that can truly help you. It avoids both extreme anxiety and passive acceptance, looking for a middle way of reacting that may actually improve the chances of a cure.

Doing for yourself—with the help of an expert.

Out of the experience of thousands of patients, Dr. Cantor talks about every emotional consequence of the cancer experience. He discusses such vital emotional issues as faith in the physician; fear of abandonment; the process of restitution; the failure of treatment; how different types of marriages and family relationships are likely to respond; handling depression, and much more. Just about everything you could ever want to know, every piece of advice you could ever need, is contained in *And A Time to Live*.

If you need help getting through your experience with cancer in someone you love, you need this book. It will help you have the kind of hope you never thought possible.

"A fine and useful book, unusual in its scope, insight, and compassion."
—ALLEN B. WHEELIS, MD.,
author of *The Seeker*

"An extraordinarily fine book . . . It is full of vitally important information and wise counsel for people who have cancer and for all who relate to them as professionals, family members, or friends."
—NEVITT SANFORD, author of
The Authoritarian Personality

AND A TIME TO LIVE
Toward Emotional Well-Being During the Crisis of Cancer
by Dr. Robert Chernin Cantor
$10.95

At your bookstore, or:

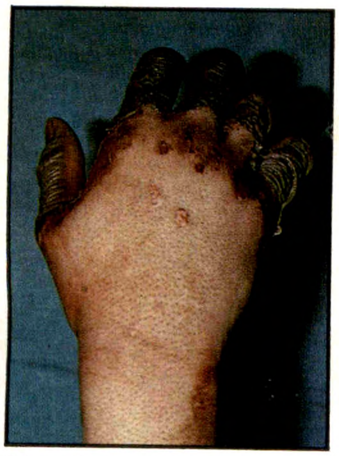
HARPER & ROW, Publishers
Attn: R. Brengel
10 East 53rd Street
New York, N.Y. 10022

Please send me ________ copies of *And A Time to Live* @ $10.95 per copy plus 75¢ for postage and handling. If not satisfied, I may return the book(s) within 10 days for a full refund. I enclose ☐ check ☐ money order in the amount of $________ total. (Please add applicable sales tax.)

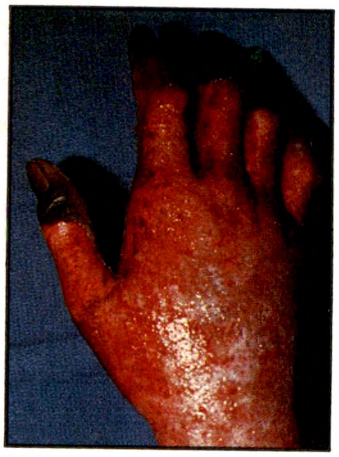
Name ________________________________
Address ________________________________
City ________________ State ________ Zip ________

NEW TECHNIQUE IN THE TREATMENT OF DEEP DERMAL HAND BURN

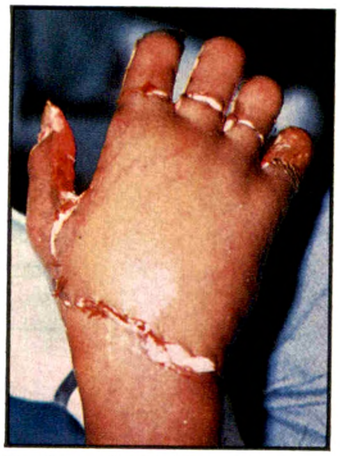
ENZYMATIC DEBRIDEMENT WITH IMMEDIATE GRAFT[1]



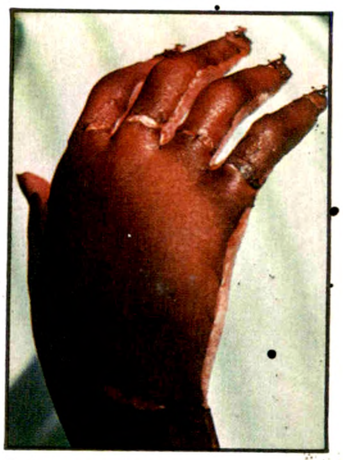
2 hours postburn on admission



24 hours postburn



Graft applied 24 hours postburn



5 days postburn

Technique:

1. Apply TRAVASE® Ointment (Sutilains Ointment, NF) upon admission (within 24 hours of burn injury).
2. Repeat every 12 hours until debridement produces punctate dermal bleeding.
3. After 24 hours, if debridement is incomplete, add an appropriate antimicrobial.
4. Graft as soon as punctate dermal bleeding is produced (within 24 to 36 hours postburn).
5. Remove dressings four days postgraft and initiate return to motion.

The use of this new technique, utilizing TRAVASE® Ointment, is an interesting development in the treatment of deep dermal hand burns. The speed of debridement and rapidity of healing obtained with TRAVASE Ointment makes this new technique possible.

Advantages:

- Preserves viable tissue
- Achieves early skin cover
- Initiates early range of motion
- Reduces likelihood of blood loss and surgery
- Shortens hospitalization and period of disability
- Minimizes hypertrophic scarring

TRAVASE® OINTMENT
(Sutilains Ointment, NF)

TRAVASE® Ointment
(Sutilains Ointment NF)

Indications: For wound debridement. TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:

Second and third degree burns.
Decubitus ulcers.
Incisional, traumatic, and pyogenic wounds.
Ulcers secondary to peripheral vascular disease.

Contraindications: Application of TRAVASE Ointment is contraindicated in the following conditions:

Wounds communicating with major body cavities.
Wounds containing exposed major nerves or nervous tissue.
Fungating neoplastic ulcers.
Wounds in women of child-bearing potential—because of lack of laboratory evidence of effects of TRAVASE Ointment upon the developing fetus.

Warning: Do not permit TRAVASE Ointment to come into contact with the eyes. If contact is made, immediately rinse with copious amounts of water, preferably sterile.

Precautions: A moist environment is essential to optimal activity of the enzyme. Enzyme activity may also be impaired by certain agents (see package insert). Although there have been no reports of systemic allergic reaction in humans, studies have shown that there may be an antibody response in humans to absorbed enzyme material.

Adverse Reactions: Consist of mild, transient pain, paresthesias, bleeding and transient dermatitis. Pain usually can be controlled by administration of mild analgesics. Side effects severe enough to warrant discontinuation of therapy occasionally have occurred.

If bleeding or dermatitis occurs as a result of the application of TRAVASE Ointment, therapy should be discontinued. No systemic toxicity has been observed as a result of the topical application of TRAVASE Ointment.

DOSAGE AND ADMINISTRATION: STRICT ADHERENCE TO THE FOLLOWING IS REQUIRED FOR EFFECTIVE RESULTS OF TREATMENT.

1. Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials which may denature enzyme or alter substrate characteristics (e.g., hexachlorophene, silver nitrate, benzalkonium chloride, nitrofurazone).
2. Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g., sodium chloride or water solutions).
3. Apply TRAVASE Ointment in a thin layer assuring intimate contact with necrotic tissue and complete wound coverage extending ¼ to ½ inch beyond the area to be debrided.
4. Apply loose wet dressings.
5. Repeat entire procedure 3 to 4 times per day for best results.

How Supplied: TRAVASE Ointment (Sutilains Ointment, NF) is supplied sterile in one-half ounce (14.2 gm) tubes. Each gram contains 82,000 casein units of proteolytic activity in a hydrophobic ointment base.

The ointment must be stored under refrigeration at 2° to 8° C (35° to 46° F).

U.S. Patent No. 3,409,719

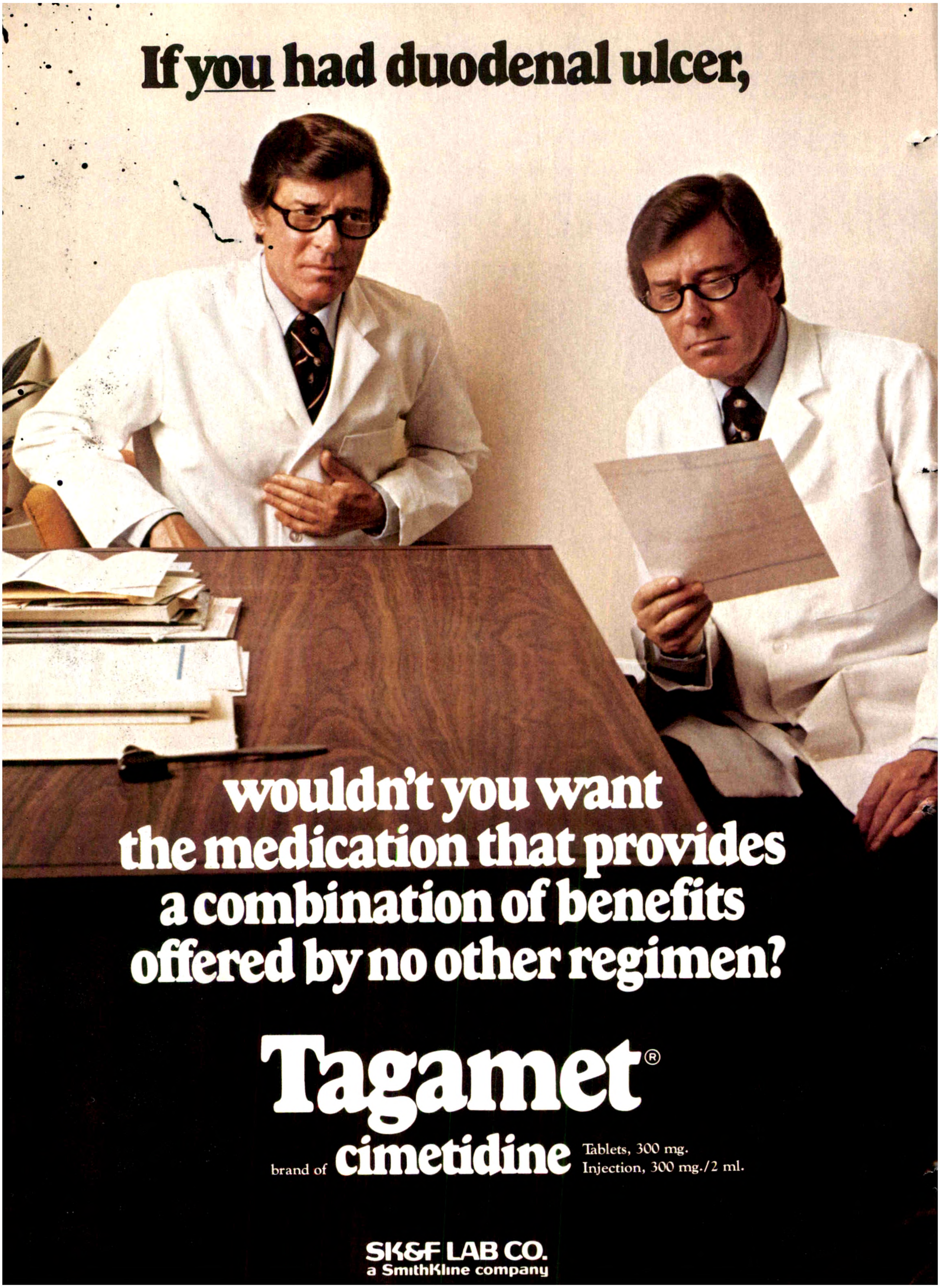
8-19-20-137A August 1976

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

© Copyright 1979 Travenol Laboratories, Inc.

---

1. Lassa R: Presentation at American Plastic & Reconstructive Surgery Meeting and Hand Society Meeting, Hollywood, FL, November, 1978.



If *you* had duodenal ulcer,

wouldn't you want
the medication that provides
a combination of benefits
offered by no other regimen?

Tagamet®

brand of **cimetidine** Tablets, 300 mg.
Injection, 300 mg./2 ml.

SK&F LAB CO.
a SmithKline company

Tagamet®

brand of **cimetidine** Tablets, 300 mg.
Injection, 300 mg./2 ml.

A unique combination of benefits for your duodenal ulcer patients

Documented effectiveness in ulcer healing and symptom relief

●

Prolonged nighttime acid suppression

●

Low incidence of side effects after use in more than 8,000,000 patients worldwide

●

Simple regimen, easy compliance

Dosage in Duodenal Ulcer

The recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been confirmed.

Concomitant antacids should be given as needed for relief of pain.

Dosage should be reduced in patients with impaired renal function.

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indications: 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: In a 24-month toxicity study in rats at dose levels approximately 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy.

Potentiation of warfarin-type anticoagulants has been observed with concomitant 'Tagamet' administration. For this reason, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when these drugs are administered concomitantly.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

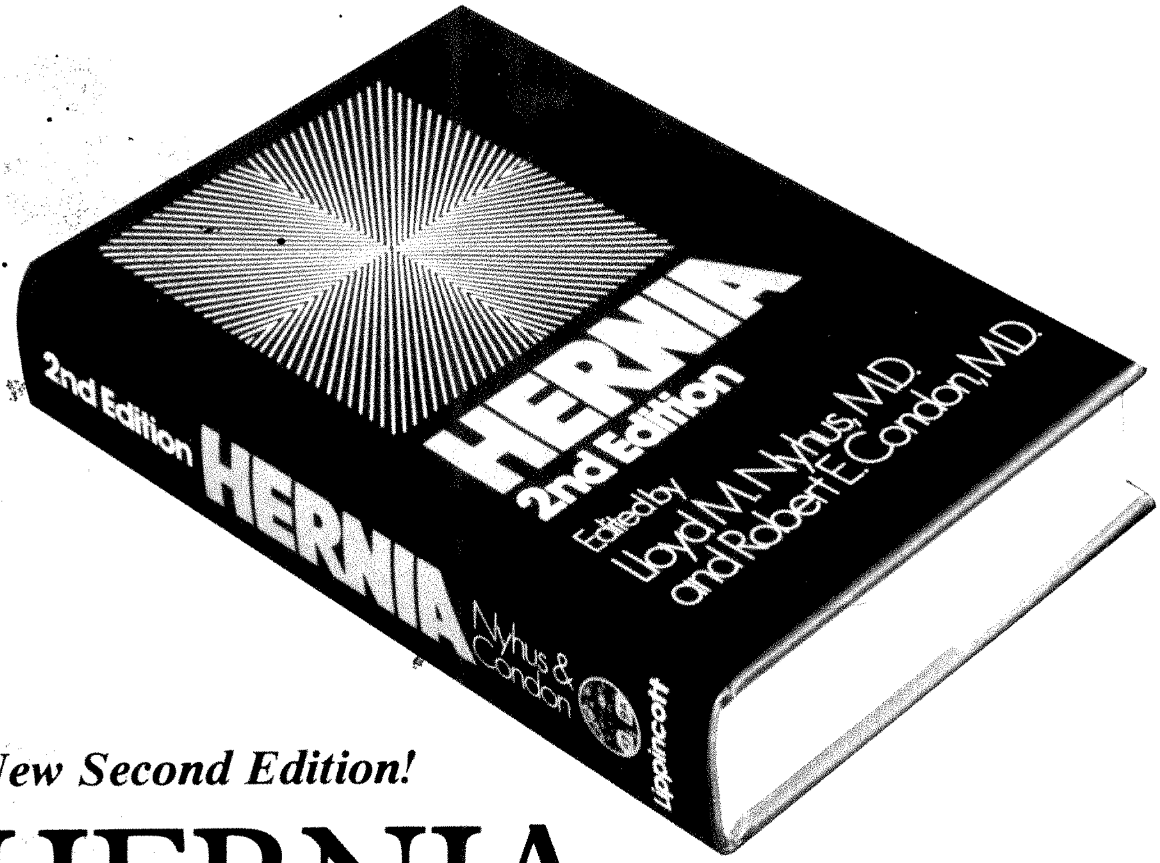
Adverse Reactions: Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of reversible confusional states have been reported, usually in elderly and/or severely ill patients. A few cases of neutropenia have been reported, but no causal relationship could be established. Increased serum transaminase and creatinine, as well as rare cases of fever and interstitial nephritis, have been reported; these cleared on withdrawal of the drug.

How Supplied: Pale Green Tablets: 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only).

Injection: 300 mg./2 ml. in single-dose vials and in 8 ml. multiple-dose vials, in packages of 10.

Date of issuance Mar. 1979

SK&F LAB CO.
a SmithKline company



New Second Edition!

HERNIA

Edited by
Lloyd M. Nyhus, M.D.
and
Robert E. Condon, M.D.

"The book to end all books on hernia" . . . "Magnificent" . . . "recommended unreservedly" . . . "a summation of today's best total hernia knowledge" are just a small sampling of the international acclaim which greeted the publication of the first edition of this major work on hernia. Dr. Nyhus has now joined with a new co-editor, the noted surgeon Dr. Robert E. Condon, to bring this tremendous opus up-to-date in a *New (2nd) Edition.*

The many additions and revisions to this classic text fulfill the editors' goal of bringing together, in one definitive volume, all established and innovative concepts of hernial etiology, diagnosis, and repair. They reflect the current emphasis on specific types of hernias and certain therapeutic techniques. For example, of special interest in this edition is the considerably expanded section on hernias of the diaphragm, which represents the only truly comprehensive review of this clinically important condition that is presently available. A helpful discussion of the Shouldice approach and experience is also included.

The popular format of the original book has been retained, giving the readers the very best, most up-to-date information in every area of hernial surgery, from world-renowned contributors. The chapters are again followed by *Special Comments* from invited experts, followed by *Editorial Comments* by the editors.

782 Pages — 457 Illustrations
2nd Edition, 1978 — $59.00

Lippincott

J. B. LIPPINCOTT COMPANY
East Washington Square • Phila., Pa. 19105

In Canada: J. B. Lippincott Company of Canada Ltd.
75 Horner Avenue, Toronto, Ontario M8Z 4X7

Please send me:
Nyhus & Condon: HERNIA 2nd Ed. $59.00

Name ______________________
Address ______________________
City ____________ State ______ Zip ______

☐ Payment enclosed (Save postage and handling) ☐ Charge and bill me (Plus postage and handling)

Also available at your medical bookstore. AS 7/79

in the progression
of advanced breast cancer

your next therapeutic step may be the safest

TABLETS, 20 mg and 40 mg

MEGACE®

(MEGESTROL ACETATE)

antiestrogenic oral progestogen

For prescribing considerations, please see last page of this advertisement.

In advanced breast cancer, regression rates comparable to those usually obtained with chemotherapy or other endocrine therapies[1,2]

MEGACE was studied in 116 patients with advanced breast cancer; there was no selection of patients based on age, menopausal status, previous therapy, or physical state—near-terminal patients were not excluded.

Of the 95 evaluable patients,[*] MEGACE induced arrest or objective regression[†] in 47 (49.5%). An additional 12 patients (12.6%) had subjective improvement.[††] [2]

MEGACE, rather than adding major adverse effects, may add subjective improvement

Patients who had had different degrees of anorexia and weight loss on entering clinical trials with MEGACE responded with increased appetite and weight gain, as well as an improved sense of well-being and amelioration of pain in the face of progressing disease.[1,2]

Serious adverse effects have not been reported in any study with MEGACE.[2] Unlike estrogens, androgens, and the antiestrogen, tamoxifen,[3-5] there have been no reports of "flares" in tumor pain, or of severe hypercalcemia in patients with bone metastases. Only a few occurrences of any adverse reactions to MEGACE have been reported. Minor or annoying side effects have been described as occurring in "...most" patients receiving tamoxifen.[6]

[*] Of the 116 patients, 21 were not evaluable due to inadequate follow-up.

[†] Definite decrease in size of half the lesions while other lesions remained static, or a decrease in half of non-osseous lesions with bone lesions static.

[††] Improved well-being, increased appetite, weight gain, and amelioration of pain in the face of progressing disease.

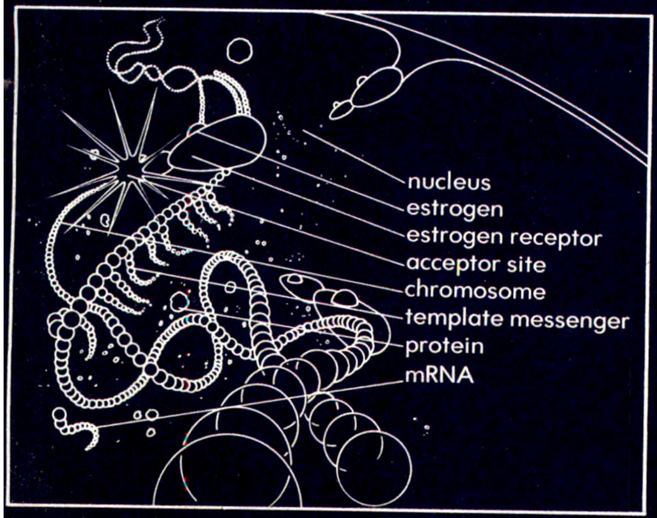
For prescribing considerations, please see last page of this advertisement.

MEGACE may help prolong the effectiveness of chemotherapy

In sequential, single, or combination therapy, a drug such as MEGACE—providing different biochemical mechanisms of action—may permit sequential use of chemotherapy by delaying or preventing acquisition of resistance by tumor cells to chemotherapeutic agents.[7] This is most important in continuing effective chemotherapy in responsive tumors.[4,6,8]

MEGACE may benefit patients at any sequence of therapy. Given after cytotoxic agents in patients with widespread metastases, MEGACE may provide remission rates comparable to those with cytotoxic therapy...plus, a respite from toxicity and time for bone marrow to recover.[1,9]

MEGACE is the only oral progestogen indicated for palliative treatment of both advanced breast and endometrial cancer



Estrogen activation of cell begins with hormone's passage into cytoplasm. This occurs with all cells, but in estrogen-sensitive cells the hormone is "attracted" by a specific protein receptor. Binding of the hormone to the receptor protein permits both to pass through the nuclear membrane and attach nonspecifically to chromatin. Hormone-receptor complex moves to a specific effector site on the chromosome, where it triggers synthesis of messenger RNA corresponding to the gene at the site. Final step is migration of mRNA to cytoplasm, where it presides over protein synthesis.*

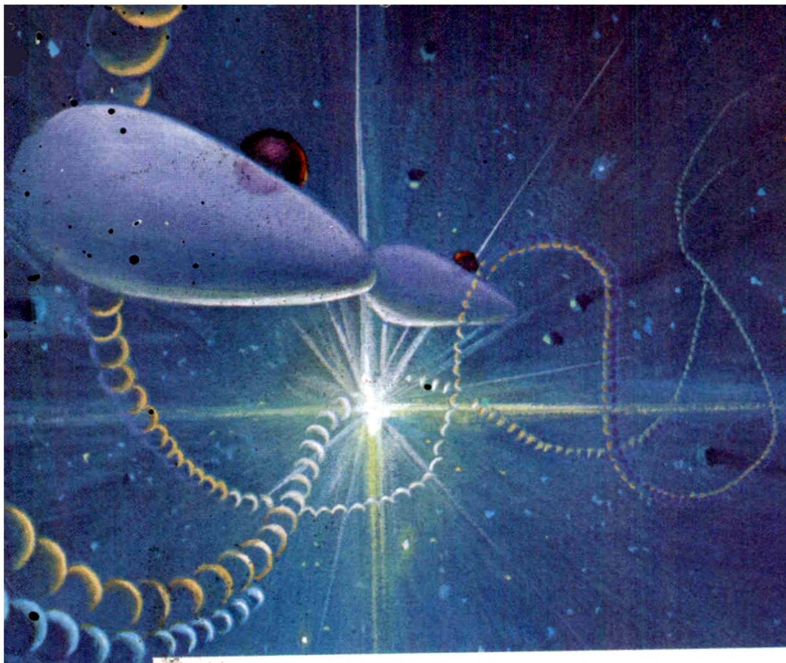
Adapted from O'Malley.[10]

TABLETS, 20 mg and 40 mg

MEGACE®

(MEGESTROL ACETATE)

MeadJohnson PHARMACEUTICAL DIVISION



TABLETS, 20 mg and 40 mg

MEGACE®

(MEGESTROL ACETATE)

Oral endocrine therapy in advanced breast cancer

May benefit patients objectively and subjectively, with unsurpassed safety

REFERENCES:

1. Ansfield FJ, Davis HL Jr, Ramirez G, et al: Further clinical studies with megestrol acetate in advanced breast cancer. *Cancer* 38:53, 1976.
2. Data on file, Mead Johnson Pharmaceutical Division.
3. Carter SK: What you can do for your patients with breast cancer. *Res Staff Phy* 25:56–64, 1979.
4. Legha SW, Davis HL, Muggia FM: Hormonal therapy of breast cancer: new approaches and concepts. *Ann Intern Med* 88:69–77, 1978.
5. Minton MJ, Cantwell BMJ, Knight RK, et al: Safety of tamoxifen. *Lancet* 1:396–397, 1978.
6. Heuson J-C: Current overview of EORTC clinical trials with tamoxifen. *Cancer Treat Rep* 60:1463–1466, 1976.
7. Canellos GP, DeViat VT, Gold GL, et al: Combination chemotherapy for advanced breast cancer: response and effect on survival. *Ann Intern Med* 84:389–392, 1976.
8. Lippman ME, Allegra JC: Current concepts in cancer: receptors in breast cancer. *New Eng J Med* 2:930–933, 1978.
9. Ansfield FJ, Davis HL Jr, Ellerby RA, Ramirez G: A clinical trial of megestrol acetate in advanced breast cancer. *Cancer* 33:907–910, 1974.
10. O'Malley BW: Hormones, genes, and cancer. *Hosp Pract* 10:65, 1965.

WARNING

THE USE OF PROGESTATIONAL AGENTS DURING THE FIRST FOUR MONTHS OF PREGNANCY IS NOT RECOMMENDED

Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion or treat threatened abortion. There is no adequate evidence that such use is effective and there is evidence of potential harm to the fetus when such drugs are given during the first four months of pregnancy.

Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion. Therefore, the use of such drugs during the first four months of pregnancy is not recommended.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[1-5] One study[4] estimated a 4.7-fold increased risk of limb reduction defects in infants exposed *in utero* to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 to 1,000.

If the patient is exposed to Megace during the first four months of pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus.

INDICATIONS

Megace (megestrol acetate) is indicated for the palliative treatment of advanced carcinoma of the breast or endometrium (i.e., recurrent, inoperable, or metastatic disease). It should not be used in lieu of currently accepted procedures such as surgery, radiation, etc.

CONTRAINDICATIONS

As a diagnostic test for pregnancy.

WARNINGS

Administration for up to 7 years of megestrol acetate to female dogs is associated with an increased incidence of both benign and malignant tumors of the breast. Comparable studies in rats and ongoing studies in monkeys are not associated with an increased incidence of tumors. The relationship of the dog tumors to humans is unknown but should be considered in assessing the benefit-to-risk ratio when prescribing Megace and in surveillance of patients on therapy.

The use of Megace (megestrol acetate) in other types of neoplastic disease is not recommended.

PRECAUTIONS

There are no specific precautions identified for the use of Megace (megestrol acetate) when used as recommended. Close, customary surveillance is indicated for any patient being treated for recurrent or metastatic cancer. Use with caution in patients with a history of thrombophlebitis.

ADVERSE REACTIONS

No untoward effects have been ascribed to Megace therapy. Reports have been received of patients developing carpal tunnel syndrome, deep vein thrombophlebitis and alopecia while taking megestrol acetate.

OVERDOSAGE

No serious side effects have resulted from studies involving Megace (megestrol acetate) administered in dosages as high as 800 mg/day.

DOSAGE AND ADMINISTRATION

Breast cancer: 160 mg/day (40 q.i.d.).

Endometrial carcinoma: 40–320 mg/day in divided doses.

At least two months of continuous treatment is considered an adequate period for determining the efficacy of Megace (megestrol acetate).

HOW SUPPLIED

Megace® is available as light blue, scored tablets containing 20 mg or 40 mg megestrol acetate in bottles of 100 tablets each.

NDC 0087-0595-01, 20 mg tablet	Bottles of 100
NDC 0087-0596-41, 40 mg tablet	Bottles of 100

References:

1. Gal I, Kirman B, Stern J: Hormonal pregnancy tests and congenital malformation. *Nature* 216:83, 1967.
2. Levy EP, Cohen A, Fraser FC: Hormone treatment during pregnancy and congenital heart defects. *Lancet* 1:611, 1973.
3. Nora J, Nora A: Birth defects and oral contraceptives. *Lancet* 1:941, 1973.
4. Janerich DT, Piper JM, Glebatis DM: Oral contraceptives and congenital limb-reduction defects. *New Eng J Med* 291:697, 1974.
5. Heinonen OP, Slone D, Monson RR, et al: Cardiovascular birth defects and antenatal exposure to female sex hormones. *New Eng J Med* 296:67, 1977.

Mead Johnson PHARMACEUTICAL DIVISION

© 1979 Mead Johnson & Company • Evansville, Indiana 47721 U.S.A.   MJL 9-4440

Evaluation and Complications of 107 Staging Laparotomies for Hodgkin's Disease

BERNARD J. URLAUB, M.D., EBERHARD MACK, M.D., F.A.C.S.

From the University of Wisconsin Center for Health Sciences, Madison, Wisconsin

From 1971–1975, 107 staging laparotomies for Hodgkin's disease were performed at the University of Wisconsin Hospitals. Forty-one per cent of patients with abnormal abdominal lymphangiograms preoperatively had abdominal nodes which were negative for Hodgkin's. Thirteen per cent of patients with negative preoperative lymphangiograms had positive nodes at staging laparotomy. Twenty-nine per cent were upstaged by laparotomy, *i.e.* assigned to a less favorable stage (II A to III A), and 11.2% were downstaged. There were no surgical mortalities. Minor surgical complications occurred in 14.9%, and major ones in 3.7%. We conclude that surgical staging for Hodgkin's disease is valuable in making an accurate diagnosis and, hence, in determining the most effective treatment.

THE IDEA OF A UNICENTRIC locus in Hodgkin's disease with a subsequent, predictable, adjacent nodal spread is no longer accepted by all investigators. Hodgkin's disease, no matter how early it is diagnosed,[1] is sometimes found on both sides of the diaphragm. Surgical staging is the most reliable method for ascertaining intra-abdominal nodal and extranodal involvement.

However, it will remain a useful tool only if staging laparotomy leads, with reasonable frequency, to a changed clinical stage and thereby to improved therapy. In addition, these benefits must not have an excessive cost in morbidity and mortality.

To help determine the efficacy of surgical staging, we examined the results in 107 staging procedures performed at our institution over a four year period.

Patients and Methods

From 1971 through 1975, 107 Hodgkin's staging procedures were performed at the University of Wisconsin Hospitals. There were 50 females and 57 males ranging in age from five years to 67 years. Median age was 24 years and mean age 29.9 years.

The 12 attending staff employed a similar staging procedure consisting of liver biopsies, splenectomy, and multiple abdominal node biopsies usually through a left paramedian incision. Bone marrow biopsies, ovarian repositionings and appendectomies were done occasionally, but not routinely. Routine prophylactic antibiotics were not used.

Results

There were no mortalities in our series. There were 20 complications in 14 patients; four patients had two complications each and one had three complications. The total rate of complications (major and minor) was 18.6% with four being considered as major (Table 1).

The majority of the complications (12 patients) occurred in Stages II B, III B, and IV B patients. However, one-third, or seven of the complications occurred in Stages I A and II A patients. One occurred in Stage I B.

The one case of deep vein thrombophlebitis was easily controlled by intravenous heparin. A 14-year-old girl bled from the splenic pedicle and short gastric vessels requiring reoperation and multiple transfusions. An uneventful recovery followed. A wound dehiscence four days postoperatively in a 34-year-old, Stage IV B male was resutured with subsequent prompt healing. A subphrenic abscess in a 21-year-old woman was drained 22 days postoperatively. This patient also had a serum amylase level of 2200 Somogyi units which promptly returned to normal following treatment.

The minor complications tabulated in Table 2 all cleared readily with standard therapy. The subcutaneous wound infections required a few extra days of hospitalization. The two cases of pancreatitis were evidenced by transient rises in serum amylase.

When prestaging lymphangiogram was compared to the intra-abdominal lymph node findings at the time of

---

Reprint requests: Eberhard Mack, M.D., University of Wisconsin Clinical Science Center, Department of Surgery, 600 Highland Avenue, Madison, Wisconsin 53792.

Submitted for publication: January 2, 1979.

0003-4932/79/0700/0045 $00.65 © J. B. Lippincott Company

TABLE 1. *Major Complications Encountered in 107 Staging Procedures*

Complication	Number of Patients
Deep vein thrombophlebitis	1
Postoperative hemorrhage	1
Wound dehiscence	1
Subphrenic abscess	1
Total	4 (3.7%)

staging, 79 of 101, or 78% confirmed the preoperative clinical stage (Table 3). Thirty-two patients had positive lymphangiograms. Therefore, 13 of 32 patients had negative node biopsies for a disagreement rate of 41%. Nine of 69 negative lymphangiograms produced positive nodes for 13% false negative lymphangiogram results. Six patients did not have nodal biopsies and are deleted from these data. Of 32 patients with positive lymphangiograms who had abdominal nodes biopsied, two had involvement of the spleen only. Of 70 patients with negative lymphangiograms, 11 had only splenic involvement.

Histologically, nodular sclerosis and mixed cellularity cell types combined form the majority of our patients with 88.8% (Table 4).

In Table 5 the histologic findings were separated into favorable (lymphocyte predominance and nodular sclerosis) and unfavorable (mixed cellularity and lymphocyte depletion) categories and then compared to the change in stage after laparotomy. In Stage I A favorable histology, 37.5% were upstaged. Combining Stage I A and II A favorable histology, we upstaged 27%. Favorable and unfavorable were upstaged 15 and 16 times, respectively. However, unfavorable histology was downstaged twice as often as favorable histology. Overall, 59.8% were correctly clinically staged whereas 40.1% were incorrectly staged preoperatively. About one-fourth of patients (28.9%) were upstaged, while 11.2% of patients were downstaged.

TABLE 2. *Minor Complications Encountered in 107 Staging Procedures*

Complications	Number of Patients
Pleural effusions	6
Pulmonary infiltrates	4
Subcutaneous wound infections	3
Superficial thrombophlebitis	1
Pancreatitis	2
Total	16 (14.9%)

TABLE 3. *Comparison of Prestaging Lymphangiogram to Abdominal Nodes at Staging*

	Abdominal Nodes		
	Positive	Negative	Spleen Pos Only
Lymphangiogram Positive	19 (32)	13 (32)	2
Per cent disagreement		40.6%	
Lymphangiogram Negative	9 (69)	60 (69)	11
Per cent disagreement	13%		

Discussion

Despite extensive preoperative evaluation to determine the clinical stage in Hodgkin's disease, staging laparotomy continues to alter the clinical stage in one-fourth to one-third of the patients in the literature reviewed.[1-3,5-8] Our own series shows a 29% surgical upstaging. Upstaging indicates the assignment of a patient to a worse prognostic stage *i.e.*, II A to III A. Downstaging implies the opposite. The lymphangiogram continues to be not only an important clinical staging tool, but also a useful guide intraoperatively to direct the surgeon to the questionably positive node bearing areas. Our accuracy rate of the preoperative lymphangiogram was 78% which correlates well with other series.[1,2,5-7] False positive results on preoperative lymphangiogram are reported as high as 67%.[5] The disagreement rate in our lymphangiograms was 41%.

These facts stress the importance of a thorough surgical laparotomy to assess the accurate stage of a patient.

The current debate as to the reliability of the preoperative lymphangiogram centers around the fact that splenic involvement and extranodal recurrences cannot be properly evaluated by this diagnostic modality.[4-6]

Some investigators believe that splenic involvement indicates hematogenous spread of the disease and therefore chemotherapy is necessary in addition to x-ray treatment.[4] One series showed that 88% of lymphangiogram-negative Stage I and II patients had splenic involvement when positive abdominal findings were present.[2] If, indeed, hematologic spread is present when the spleen is positive then staging laparotomy on

TABLE 4. *Histopathologic Type*

	Number	Per Cent
Nodular sclerosis	51	48
Mixed cellularity	44	41
Lymphocyte predominance	9	8
Lymphocyte depletion	3	3
Total	107	100

TABLE 5. *Histology and Surgical Change*

	Upstage					Downstage	
	IA	IIA	IIIA	IIB	IIIB	IIIA	IIB
Favorable histology*	3 (8)	6 (25)	0 (4)	3 (11)	3 (12)	3 (4)	1 (12)
Unfavorable histology†	0 (4)	5 (15)	3 (12)	5 (7)	3 (9)	4 (12)	4 (9)
Total	3 (12)	11 (40)	3 (16)	8 (18)	6 (21)	7 (16)	5 (21)
Per cent	25%	27.5%	18.8%	44.4%	28.6%	43.8%	23.8%

*F.H. = L.P. + N.S. †*U.H.* = M.C. + L.D.

1. Stages not listed above remained at preoperative stage.
2. Numbers in parentheses are totals in that clinical preoperative stage.

patients with lymphangiogram negative Stage I and II is helpful because we are thereby upstaging Stages I and II. Furthermore, laparotomy changes the treatment approach by determining extranodal spread *i.e.*, to spleen, liver, etc. In our series we have upstaged 27% of our Stage I and II patients with favorable histology. Of the 69 lymphangiogram negative Stage I and II patients in our series 50% or 6 of 12 had positive spleens when the abdomen was positive. This is less than in another series from M. D. Anderson Hospital, but is significant.[2]

A recent addition to the clinical (prelaparotomy) staging has been the use of laparoscopy to inspect the liver and obtain biopsies of involved liver areas, thereby assigning a patient to Stage IV and thus avoiding a standard staging laparotomy. In our series of 107 staging laparotomies, there were only nine patients with positive liver findings out of the total group of 36 where the preoperative lymphangiogram was read as positive. This would mean that preoperative laparoscopy would have been of value in only 8% of the cases. Such a low diagnostic yield is even worse in the lymphangiogram negative patients where from the total group of 70 only three had positive liver findings, equivalent to only 3% yield of laparoscopy. Therefore, we cannot recommend preoperative laparoscopy as a valuable diagnostic adjunct in the Hodgkin's patient.

Some authors feel that the rate of surgical complications from the staging laparotomy increases in patients over the age of 50 and suggest that these patients should not be staged.[5,8] Our study does not support such age limitation since all of our complications occurred in patients under the age of 50. But, in agreement with the same author, we also found eight of nine patients over age 50 years to have unfavorable histology, namely mixed cellularity.[5]

Even our pediatric and adolescent age group compares more favorably in regard to complications with other reported series.[3] Our overall complication rate of 18.6%, including 14.9% minor and 3.7% major cases, without a single mortality indeed is quite acceptable and correlates well with other series in the literature.[1,3,6,7,9,10] Therefore, we feel that the surgical staging of Hodgkin's disease plays a major role in accurate assessment of a patient's stage and continues to be warranted.

References

1. Andrassy, R. J.: Laparotomy for Staging of Hodgkin's and Non-Hodgkin's Lymphoma. Surg. Gynecol. Obstet., 114:639, 1977.
2. Gamble, J. F.: Influence of Staging Celiotomy in Localized Presentations of Hodgkin's Disease. Cancer, 35:817, 1975.
3. Hays, D. M.: Hodgkin's Disease (Staging Lap in Childhood). Arch. Surg., 106:507, 1973.
4. Hellman, S.: Current Studies in Hodgkin's Disease "What Laparotomy had Wrought." N. Engl. J. Med., 290:894, 1974.
5. Hermreck, A. S.: The Staging of Hodgkin's Disease. Am. J. Surg., 130:639, 1975.
6. Meeker, W. R., Jr.: Critical Evaluation of Laparotomy and Splenectomy in Hodgkin's Disease. Arch. Surg., 105:222, 1972.
7. Paglia, M. A.: Surgical Aspects of Laparotomy and Splenectomy in Hodgkin's Disease. Am. J. Roentgenol. Radium Ther. Nucl. Med., 117:12, 1973.
8. Schwartz, S. I.: Symposium on Surgical Staging of Hodgkin's Disease. Contemp. Surg., 5:68, 1974.
9. Slavin, R.: Complications from Staging Laparotomy for Hodgkin's Disease. Natl. Cancer Inst. Monog., 36:457, 1973.
10. Smith, M. D.: Exploratory Laparotomy for Staging in Hodgkin's Disease. Am. J. Surg., 124:811, 1972.

Regeneration of Human Liver After Hepatic Lobectomy Studied by Repeated Liver Scanning and Repeated Needle Biopsy

TIEN-YU LIN, M.D.,* CHUE-SHUE LEE, M.D.,* CHIOU-CHIANG CHEN, M.D.,* KUONG-YI LIAU, M.D.,*
WEN-SHIH-JEN LIN, M.D.†

Regeneration of the residual lobe of the liver after hepatic lobectomy in humans was studied by repeated liver scanning in seven noncirrhotic and three cirrhotic patients. Each patient was studied for several months during the study which lasted from 1–12 years. Regeneration was apparent in noncirrhotic liver remnants following hepatic lobectomy. In the case of a long standing, space occupying lesions such as benign giant cysts, the liver remnant would complete its regeneration process rather early, usually within a few months of hepatic lobectomy. In hepatoma cases, however, regeneration of the residual lobe after hepatic resection usually took five or six months for completion. On the contrary, no definite increase in the size of the liver remnant was seen on repeated liver scanning in cirrhotic patients. Histologic study of the residual lobe was repeated on needle biopsy specimens in two noncirrhotic and four cirrhotic patients. Regenerative hyperplasia of liver cells with large hyperchromatic, or double nuclei never seen in the preresection liver appeared in the liver remnant five, 11, and 27 days after hepatic lobectomy in noncirrhotic patients. In cirrhotics, however, there were no histologic changes between the preresection liver and the postresection remnant studied three, five, 15, 40 days or even two years and 8 months after hepatic lobectomy.

From the Departments of Surgery and Pathology, National Taiwan University Hospital, Taipei, Taiwan, R.O.C.

ALTHOUGH REGENERATION of the liver after extensive hepatic resection does not occur as rapidly in humans as in small animals, Pack et al.[5] proved marked regenerative hyperplasia of the liver remnant while performing a second-look exploration or required secondary operation in four patients who underwent extensive right hepatic lobectomy for cancer. They found that the lateral segment of the left lobe of the liver was enlarged to twice its normal size two and a half months after the operation. In the other case explored five months after initial resection, the lateral segment extended across the entire cupola of the diaphragm and occupied the right upper abdomen.

Another two cases re-explored 21 and 24 months respectively after extensive right hepatic lobectomy demonstrated that the lateral segment of the left lobe was normal in color and consistency and had increased its size to that of an intact whole liver. Histologic examination of the liver in the latter two cases (21 and 24 months after operation) showed normal liver tissue with evidence of marked bile duct proliferation.

Bengmark[2] also reported a case showing regeneration of the liver remnant to normal size at the time of second-look exploration one year after an extensive right hepatic lobectomy. McDermott et al.[4] studied the regeneration by repeated liver scanning with rose bengal ragged with I^{131} in two cases after an extended right hepatic lobectomy and concluded that restoration of normal liver mass had occurred within 6 months. Starzl et al.[6] also treated their patients with extensive right hepatectomy (85–90% resection). Repeated liver scanning with ^{99m}technetium disclosed that only a tiny fragment of the liver was visualized two days after operation. Regeneration began one month later and was still evident at the sixth postoperatively, but no further evidence of regeneration was seen on liver scanning taken 13 months after operation. Arousen, Bengmark et al.[1], however, followed regeneration after hepatic lobectomy in two cases of blunt liver injury with repeated liver scanning and found that the liver did not seem to be completely restored to normal size 6 months after operation.

Lin et al.[3] studied the regeneration of human liver in six noncirrhotic and five cirrhotic hepatoma patients by applying metal clips around the margins of the liver remnant at the time of hepatic lobectomy. The size of liver remnant was recorded weekly by x-ray and occasionally by liver scanning. These procedures showed

---

* Department of Surgery.

† Department of Pathology.

Reprint requests: Tien-Yu Lin, M.D., Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan, R.O.C.

Submitted for publication: November 6, 1978.

0003-4932/79/0700/0048 $00.80 © J. B. Lippincott Company

the liver remnant enlarged in periodic way definitely from the third week after hepatic lobectomy in noncirrhotic group, whereas increase in the size of the liver remnant was not noted in cirrhotic group.

The purpose of this paper is to study the regeneration of noncirrhotic and cirrhotic human liver remnants after hepatic lobectomy by repeated liver scanning in collaboration with repeated needle biopsy of the liver.

Materials and Methods

Seven noncirrhotic patients were studied by repeated liver scanning with ^{99m}technetium after hepatic lobectomy for a period of 8 months to 12 years. Two were repeatedly needle biopsied after operation for histologic study of the liver remnant. Of the seven noncirrhotics, three were lobectomized on the right lobe for benign giant cyst of the liver, four were lobectomized, three on the right and one on the left lobe, for primary carcinoma of the liver.

Another six patients who underwent hepatic lobectomy for primary carcinoma of the liver were associated with liver cirrhosis. Three were studied over a one and a half year period for regeneration of the liver remnant by repeated liver scanning. Four of the six cases were studied histologically by repeated needle biopsy of the liver remnant at 3, 5, 15, 40 days and 2 years and 8 months after left hepatic lobectomy.

Study of the metabolic function of cirrhotic and noncirrhotic human livers after hepatic lobectomy was not included in this paper, as they had been reported previously by Lin et al.[3]

Results

Regeneration of the Liver Remnant in Noncirrhotics and Cirrhotics Studied by Repeated Liver Scanning

Three cases of benign giant liver cyst in noncirrhotic group were repeatedly aspirated and infected before coming to surgery. At operation the cysts contained 3000–4000 cc of chocolate colored fluid and had almost entirely replaced the right lobe which remained merely as a thin layer of liver tissue around the cyst. The left lobe was larger than usual (Fig. 1). Repeated liver scanning after right hepatic lobectomy in these three cases showed that the remaining left lobe had restored to maximum size within three months. No further enlargement of the liver remnant was seen in later scanning (Fig. 1).

Four patients with hepatoma in the noncirrhotic group were seen for two or three months after manifestation of their initial symptoms. At laparotomy three patients showed massive type hepatoma in the right lobe, of which part of the normal liver tissue was still preserved. The left lobe looked normal in size and in appearance. Repeated scanning after hepatic lobec-

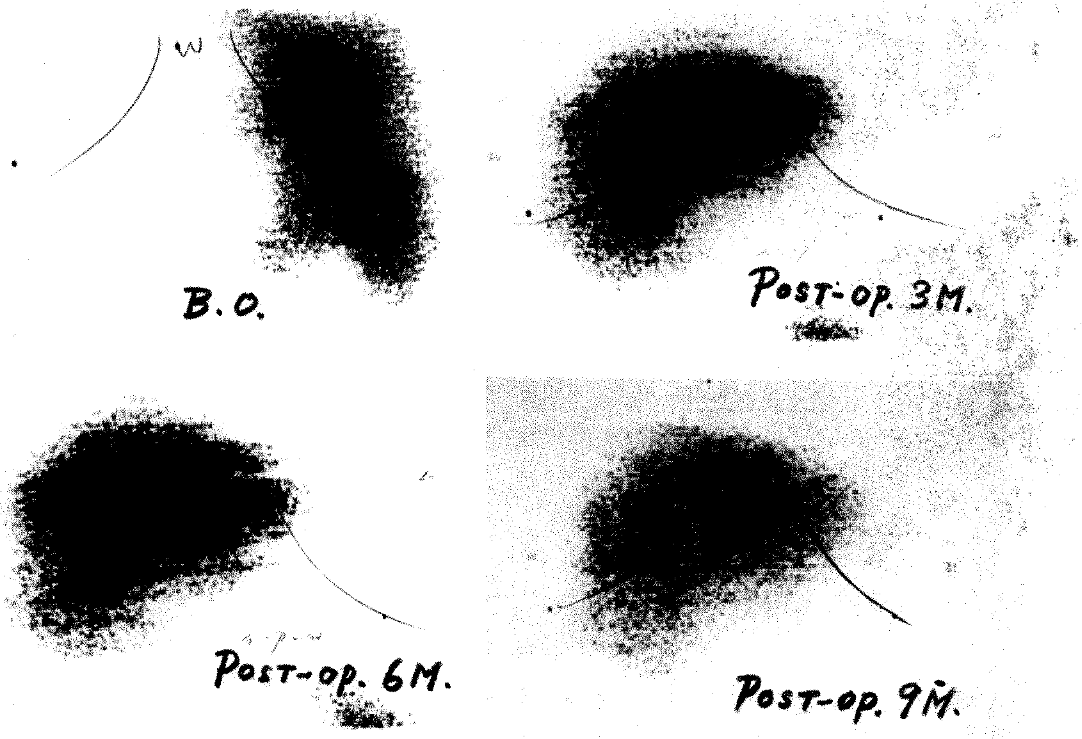


FIG. 1. The remaining left lobe returned to maximum size by the third postoperative month in a case of noncirrhotic benign giant cyst. The liver remnant scanned at six and nine months after right hepatic lobectomy showed no further enlargement.

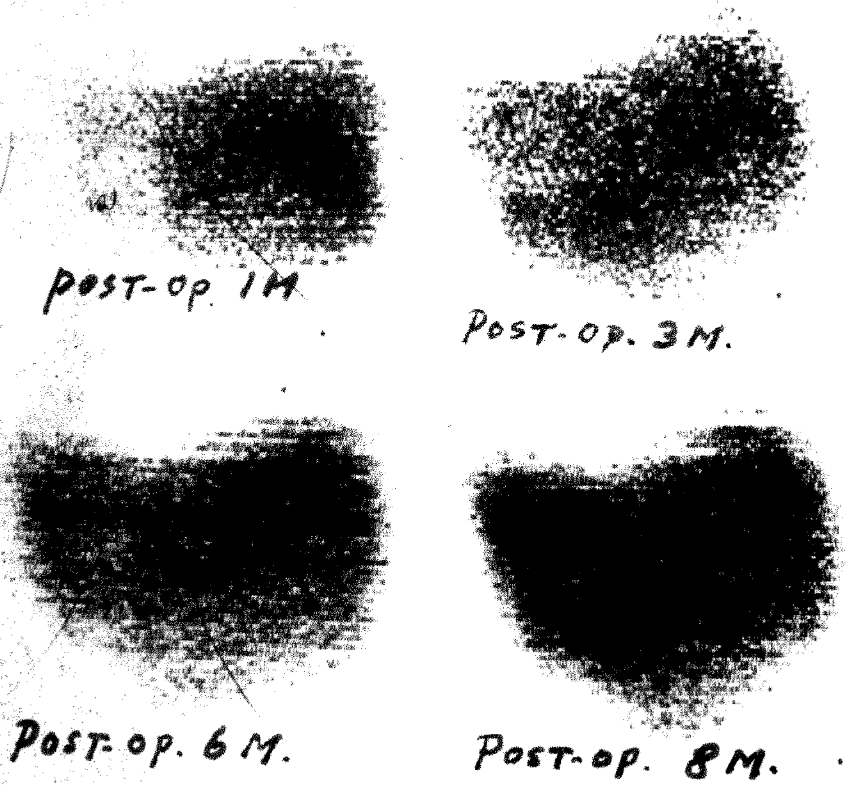


FIG. 2. The change in the size of residual left lobe after right hepatic lobectomy for a noncirrhotic hepatoma. The liver remnant reached maximum size at six months postoperatively. The liver scan taken eight months after operation shows no further increase in the size of the liver remnant.

tomy in these four patients revealed that increase in the size of the residual lobe was evident (especially marked in the right hepatectomized cases) shortly after hepatic lobectomy. The liver remnant reached maximum size on the scan within five or six months and remained unchanged thereafter (Fig. 2). In other words, the residual lobe in patients with noncirrhotic hepatoma seemed to have restored to a completed size within five or six months after operation.

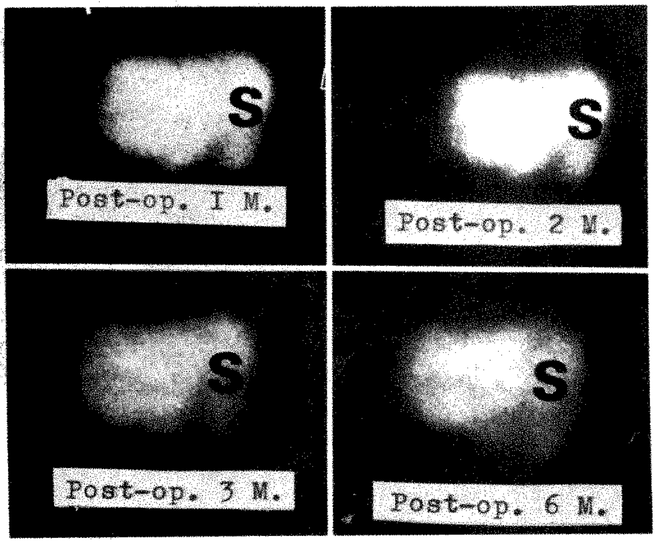


FIG. 3. Liver scan in a case of cirrhotic hepatoma in which a right hepatic lobectomy was performed. The remaining cirrhotic left lobe showed no remarkable increase in size either at one, two, three and six months after operation. The spleen (S) is enlarged.

In the cirrhotic group of two patients with left lobe hepatoma, the size of the residual right lobe scanned at six months and even one year and two months after left hepatic lobectomy remained stationary in size. In another cirrhotic patient with right lobe hepatoma, the residual left lobe scanned at one, two, three and six months after right hepatic lobectomy was consistently small and without conceivable change on the scanograms (Fig. 3).

Histology of the Residual Liver Tissue Studied by Repeated Needle Biopsy

The main pathological changes were summarized in Table 1.

Cirrhotic group. All four cases showed marked cirrhosis at hepatic lobectomy. There were formations of septa and pseudolobules, regeneration nodules (Fig. 4a) an increased number of bile ducts in portal areas and newly formed septa in all sections. The regenerating liver cells were larger than usual with an abundant,

TABLE 1. *Histological Finding of the Liver and the Liver Remnants*

Pathological changes / Cases	Pseudo-lobule	Increased Bile Ducts	Regen-eration Nodules	Enlarged Liver Cells	Hyper-chromatic of Double Nuclei	Basophilic Cytoplasm	Fatty Metamorphosis	Remarks
				Cirrhotic Group				
Case 1								
Preresection	+	+	+	+	+	+		Fig. 4a
3 days Postoperation	+	+		+	+	+	+	Fig. 4b
Case 2								
Preresection	+	+	+	+	+			
5 days Postoperation	+	+		+	+	+		
15 days Postoperation	+	+	+	+	+			
Case 3								
Preresection	+	+	+	+	+			
40 days Postoperation	+	+	+	+				
Case 4								
Preresection	+	+	+	+	+			Fig. 5a
2 yrs & 8 m. Postoperation	+	−	−	+	+			Fig. 5b
				Noncirrhotic Group				
Case 5								
Preresection	−	−	−	−	±			Fig. 6a
5 days Postoperation		+	+	+	+		+	Fig. 6b
Case 6								
Preresection	−	−	−	−	−	−	−	
11 days Postoperation		+		+	+	+		
27 days Postoperation				+	+			

clear or slightly granular cytoplasm with large, hyperchromatic nuclei. Double nuclei were common. The nearby normal liver tissue was often atrophic due to compression by these nodules (Fig. 5a).

In all needle biopsy specimens following hepatic lobectomy (regardless of the length of the interval from the time of lobectomy) the liver was cirrhotic and similar to the previous examination. Formation of septa and pseudolobules was again evident (Figs. 4b and 5b). In addition, they revealed groups of enlarged liver cells with abundant cytoplasms and common double nuclei.

In the second (Case 2) and the third cases (Case 3), there was evidence of cirrhosis with regeneration nodules in both the preresection and postbiopsy specimens.

In conclusion evidence of cirrhosis continues to exist in needle biopsy specimens regardless of the interval length (ranging from three days, five days, 15 days, 40 days or even to 2 years and 8 months) after hepatic lobectomy in the cirrhotic group.

Noncirrhotic group. Two cases were included in the noncirrhotic group. The first patient (Case 5) underwent needle biopsy five days after a right hepatic lobectomy and the second patient (Case 6) had two needle biopsies 11 and 27 days after the left hepatic lobectomy respectively.

The nontumorous livers at hepatic lobectomy in both patients were found to be normal in lobular structure and in appearance of liver cells (except for a few double nuclei in case 5, Fig. 6a). The regeneration nodule examined by needle biopsy was remarkable in Case 5 (Fig. 6b), while in Case 6 regenerative changes were evidenced by groups of enlarged liver cells with basophilic cytoplasm and hyperchromatic or double nuclei.

Hepatic regenerative activity in the noncirrhotic group was evident in the needle biopsy specimens after hepatic lobectomy (especially in Case 5 which was thought to be due to a right hepatic lobectomy yet regeneration took place in the remained small left lobe.

Discussion

The study of human hepatic regeneration is not as easy as in animal experiments. In humans regeneration of the residual lobe may be in evidence second or third re-exploration after major hepatic resection. Pack, et al.[5] reports an instance similar to this during a second look exploration or at required secondary operation. In order to study the rate of regeneration, Lin et al.[3] applied metal clips around the margin of the liver remnant at the time of hepatic lobectomy and followed the size of the liver remnant with weekly x-rays. McDermott, et al.,[4] Aronsen, Bengmark, et al.[1] and Starzl et al.[6] studied the regeneration of a liver remnant by repeated liver scanning. In this series the rate of regeneration was also studied by repeated liver scanning at one, three, four, five, six, seven, ten months and 1 year or even up to 12 years after major hepatic resection.

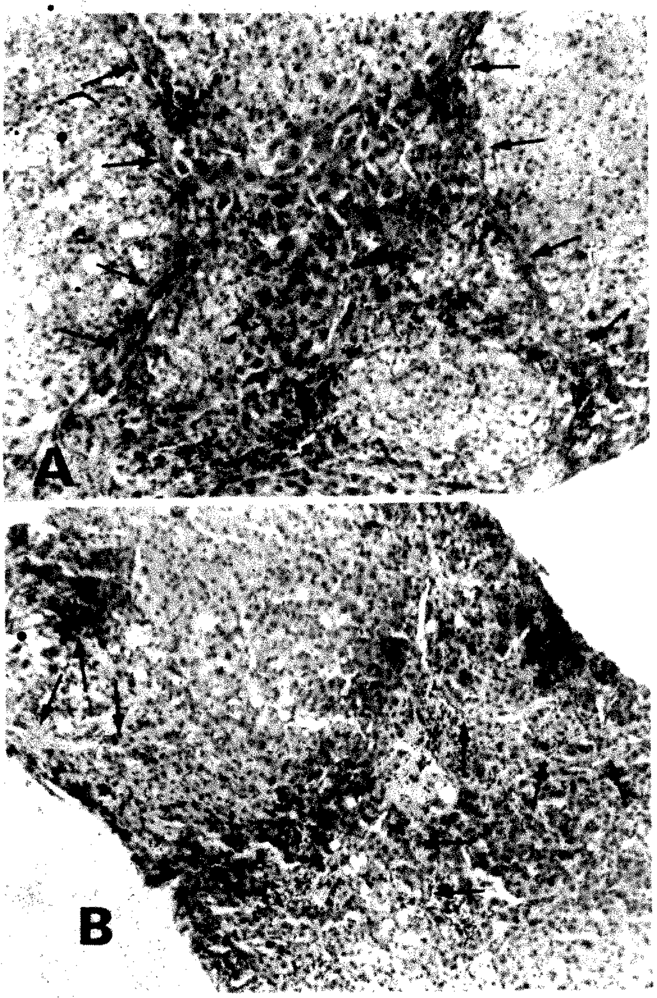


Fig. 4. (A) Newly formed septa (arrows) and regeneration nodules (×100) of preresection cirrhotic liver and (B) slender septa (arrows) and pseudolobules of the remnant liver of the same patient (Case 1) three days after left hepatic lobectomy (×100).

It is quite clear that a cirrhotic liver remnant never shows a postoperative increase in size even after one year. In contrast, a noncirrhotic liver remnant does increase in size.

When an hepatic lobe (especially the right lobe or an extended right hepatic lobe) is removed portal flow to the liver remnant will be increased immediately. Accordingly, in case of major hepatic lobectomy, the remaining noncirrhotic left lobe will immediately increase its bulk due to vascular engorgement and edema. However, the new circumstances created by hepatic lobectomy can not be immediately adjusted by a cirrhotic liver remnant and as a result will increase portal pressure. In the author's series of 33 hepatic lobectomies for cirrhotic hepatoma, two patients resulted in ruptured esophageal varices, one on the third and the other on the seventh day after right hepatic lobectomy. The ruptures were probably due to this increased portal pressure.

The increase in the size of the residual lobe of noncirrhotics seen in the later stage is, however, due to true regenerative hyperplasia which will contribute to the restoration of normal liver function. In fact Vajrabukka et al.[8] had found histologic evidence of regenerative hyperplasia including increased mitotic activity within three days after partial hepatectomy for blunt injury of a normal liver. In our series we also found remarkable regenerative nodule or enlarged liver cells with basophilic cytoplasm and hyperchromatic or double nuclei in the biopsy specimens taken from the noncirrhotic liver remnant on the fifth, eleventh and twenty-seventh postoperative days.

As to regeneration of cirrhotic liver tissue after hepatic lobectomy, although Valdoni et al.[7] reported

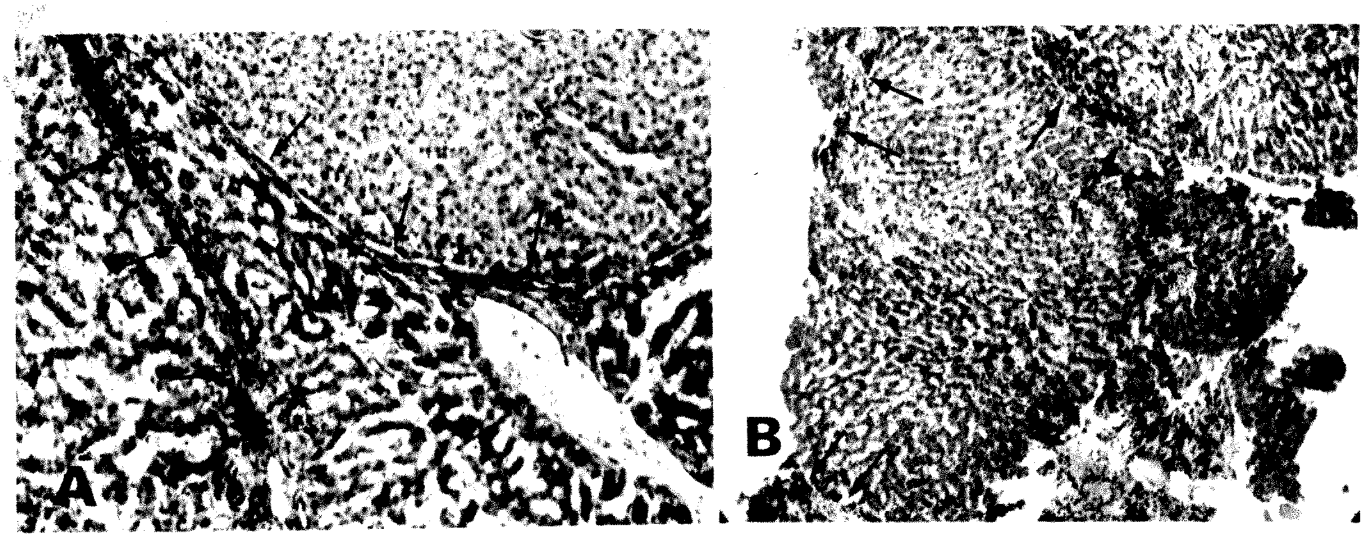


Fig. 5. (A) Formation of septa (arrows), pseudolobules and one regeneration nodule (×100) of preresection cirrhotic liver and (B) slender septa (arrows) and pseudolobules of the remnant liver of the same patient (Case 4) two years and eight months after left hepatic lobectomy (×60).

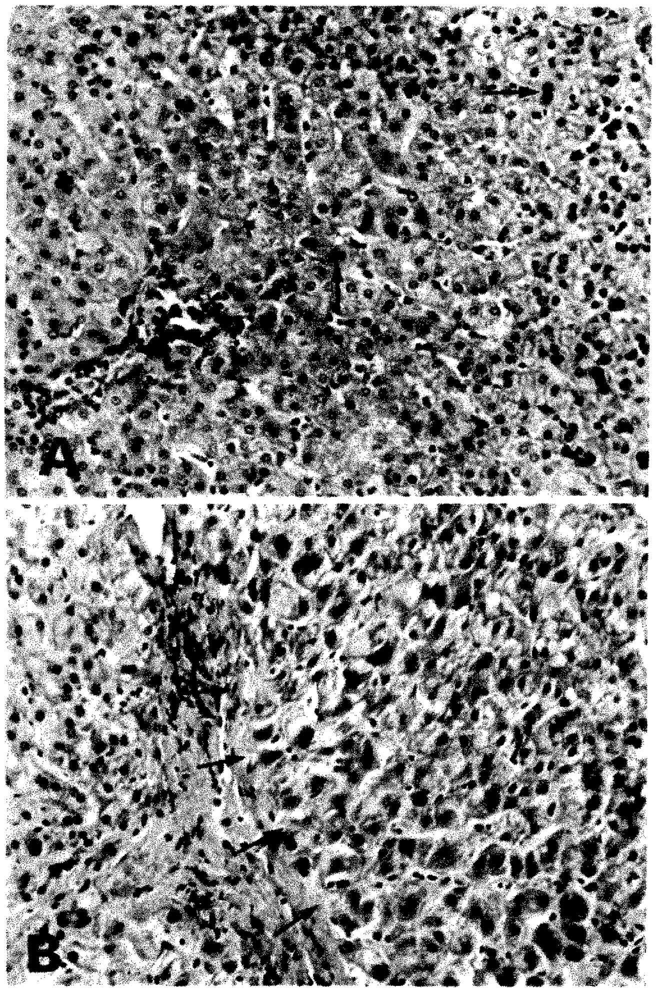


Fig. 6. (A) Normal liver structure with a few cells with double nuclei (arrows) (×200) of preresection noncirrhotic liver and (B) a regeneration nodule (arrows) (×200) appeared in the liver remnant of the same patient (Case 5) five days after right hepatic lobectomy.

marked hypertrophy of the residual liver, an histologically marked increased of the islands of liver parenchyma and a thinning of fibrous bands in a cirrhotic patient who died 21 days after partial hepatectomy, we failed to see any change in size of cirrhotic liver remnant by repeated liver scanning and by metal crips study.[3] Histologic examinations of the cirrhotic liver remnant obtained by repeated needle biopsies in our series also showed that cirrhosis persisted regardless of the length of time that elapsed after hepatic lobectomy. Moreover 39.3% of 33 hepatic lobectomies for hepatomas associated with cirrhosis in our series developed hepatic failure. This was particularly true when a right lobectomy was performed as 66.6% of the patients died of hepatic failure. A few cirrhotic hepatoma patients survived left hepatic lobectomy and remained free from cancer and in good condition for one and half a year to 2 years and 8 months. Nevertheless their liver functions still showed high level of Bromsulphalein retention. Therefore, it is difficult to say whether the cirrhotic liver remnant will normalize impaired liver function after hepatic resection.

The time difference in completing liver regeneration between the group of liver cyst patients and noncirrhotic hepatoma patients, might be explained as follows. A nonparasitic liver cyst is a benign disease. It grows very slowly and may take 1–3 years or more to totally occupy the right lobe. Consequently, the left lobe will have enough time to adapt to the increased blood flow and may already have had some regenerative hyperplasia before hepatic lobectomy. This is probably the reason why the remaining left lobe regenerates within three months after right hepatic lobectomy in cyst patients. In hepatoma patients the hepatoma grows very quickly. Usually it takes only two or three months before the mass becomes so large that surgery is indicated. During this short period the nonaffected lobe may have little chance to adapt to the increasing blood flow. This may be the reason why, in hepatoma patients, the remaining left lobe takes a longer time to complete the regenerative process. In the same respect, Aronsen, Bengmark et al.[1] reported that the normal liver did not seem to be completely restored to normal size six months after operation. They studied regeneration by repeated liver scanning in two patients who had had liver resection for blunt injuries. A normal liver always has equal blood flow to each lobe, so there is no reason for any lobe to undergo a regenerate process before liver resection. Therefore, unlike the cases of either long- or short-term disease, the normal liver may need more time to complete regeneration after hepatic resection.

References

1. Aronsen, K. F., Bengmark, S., Dahlgren, S., et al.: Liver Resection in the Treatment of Blunt Injuries to the Liver. Surgery, 63:236, 1968.
2. Bengmark, S.: Liver regeneration. *In* Pack, G. T. and Islami, A. H. (eds.) Recent Results in Cancer Research, Tumors of the Liver, New York. Springer-Verlag, 1970. p. 204.
3. Lin, T. Y. and Chen, C. C.: Metabolic function and Regeneration of Cirrhotic and Noncirrhotic Livers After Hepatic Lobectomy in Man. Ann. Surg., 162:959, 1965.
4. McDermott, W. V., Jr., Greenberger, N. J., Isselbacher, K. J. and Weber, A. L.: Major Hepatic Resection: Diagnostic Techniques and Metabolic Problems. Surgery, 54:56, 1963.
5. Pack, G. T., Islami, A. H., Hubbard, J. C. and Brasfield, R. D.: Regeneration of Human Liver After Major Hepatectomy, Surgery, 52:617, 1962.
6. Starzl, T. E., Putnum, C. W., Groth, C. G., et al.: Alopecia, Ascites and Incomplete Regeneration After 85 to 90 per cent Liver Resection. Ann. Surg., 129:587, 1975.
7. Valdoni, P., Messini, M., Ricci, G. and Mancuso, M.: La Resezione Epatica Quale Impulso Rigenerativo Nella terapia Della Cirrosi, Epatologia, 3:1, 1957.
8. Vajrabukka, T., Bloom, A. L., Sussman, M., et al.: Postoperative Problems and Management After Hepatic Resection for Blunt Injury to the Liver, Br. J. Surg., 62:189, 1975.

Five Year Study of Tissue Reaction to Synthetic Sutures

R. W. POSTLETHWAIT, M.D.

Sutures were implanted in the abdominal wall muscles of rabbits and specimens recovered at intervals from six months to five years. Tissue reaction around Nylon and Dacron® was minimal. The reaction to Teflon® coated Dacron was increased because of shedding of the Teflon. The polypropylene sutures showed fragmentation in 4% of the sutures examined and the perisutural formation of bone, cartilage or both in 2.6%.

From the Department of Surgery, Veterans Administration Medical Center and Duke University Medical Center, Durham, North Carolina

A PREVIOUS STUDY[2] of the tissue reaction to sutures over a period of two years implantation showed occasionally fragmentation of the polypropylene material. For this reason, the study was repeated but the period of observation extended to five years.

Methods

Size 3-0 monofilament nylon, monofilament polypropylene, multifilament Dacron®, and Dacron coated with Teflon® were used. The implantation technique has been previously described.[2] Briefly, the abdominal wall musculature of the rabbit was exposed and the test suture inserted intramuscularly in three loops, the ends being tied loosely. Autopsy was performed at intervals from six months to five years after implantation, Tissue was removed to include a cross section of the sutures, fixed and stained with hematoxylin and eosin.

Results

Table 1 shows the number of animals for each time interval and the number of sutures examined. The latter was less than anticipated but synthetic sutures cause problems in sectioning and the suture material would not be retained. Although the sites of sutures were easily identified, only those with retained suture were counted.

Detailed descriptions of tissue reaction to sutures have been published earlier[2,3] and will only be described very briefly. Nylon causes the least tissue response and is usually surrounded by a thin rim of fibrous tissue (Fig. 1). Dacron usually remains compact, has a slightly wider connective tissue zone and shows a few mononuclear cells near the suture. The Teflon coated Dacron differs only in that the teflon is shed from suture and stimulates its own reaction of histocytes and lymphocytes.

Polypropylene in most sections shows a reaction similar to that of nylon. Of the 351 polypropylene sutures examined, however, 14 or 4% showed some fragmentation of the suture (Fig. 2). In addition, nine sutures (in different animals) showed formation around the suture of bone, cartilage, or both (Fig. 3). Five sutures had both fragmentation and bone–cartilage deposition.

Discussion

No explanation for either the fragmentation of polypropylene or the heterotopic bone–cartilage formation is apparent.

Liebert and his associates[1] studied the chemical changes after subcutaneous implantation in hamsters of filaments of polypropylene, one with and one without antioxidants. Degradation of the polypropylene without antioxidant began within a few days by an oxidation process. They note when the hydroperoxides first formed begin to decompose, chain scission occurs, causing carbonyl groups to form. Rapid oxidation then follows, causing a sharp increase in carbonyl content and a significant loss of tensile properties. While this or another chemical change may be involved, no greater loss in breaking strength occurred in our study compared with the other materials, and the manufacturer states no antioxidants are used. In addition, fragmentation was found in only one of every 13 of the animals.

A limited survey of the literature indicates that little is known about heterotopic ossification. Rhone and Horowitz[4] in their review, while noting the exact mechanism is unclear, list the following conditions

---

Reprint requests: R. W. Postlethwait, M.D., Department of Surgery, V. A. Hospital, Durham, North Carolina 27705.

Supported in part and sutures provided by Ethicon, Inc.
Submitted for publication: January 12, 1979.

0003-4932/79/0700/0054 $00.70 © J. B. Lippincott Company

TABLE 1.

Time Months	No. Animals	Dacron No. Sutures	Nylon No. Sutures	Teflon-coated No. Sutures	Teflon-coated No. Shed	Polypropylene No. Sutures	Polypropylene No. Fragment	Polypropylene No. Bone
6–11	21	62	50	65	24	33	2	1
12–17	32	105	66	119	37	64	5	5
18–23	25	83	57	86	8	49	3	1
24–29	31	100	75	107	25	63	1	2
30–35	17	48	43	57	13	[illegible]	1	0
36–41	15	45	47	57	16	28	1	0
42–47	9	28	22	22	7	8	0	0
48–53	2	9	5	4	0	7	0	0
54–59	2	6	4	8	0	5	0	0
60	29	79	66	104	46	58	1	0
Total	183	565	435	629	176	351	14	9

which appear to be necessary: formation of a proliferating connective tissue, liberation of calcium in the vicinity of this tissue, reduced viability of cells and an adequate blood supply. They indicate that other work has suggested that an alkaline pH, neutral sugars, acid polysaccharides, and necrosis may play important roles. An inducing substance has also been suggested but not demonstrated. No prior description of bone or cartilage

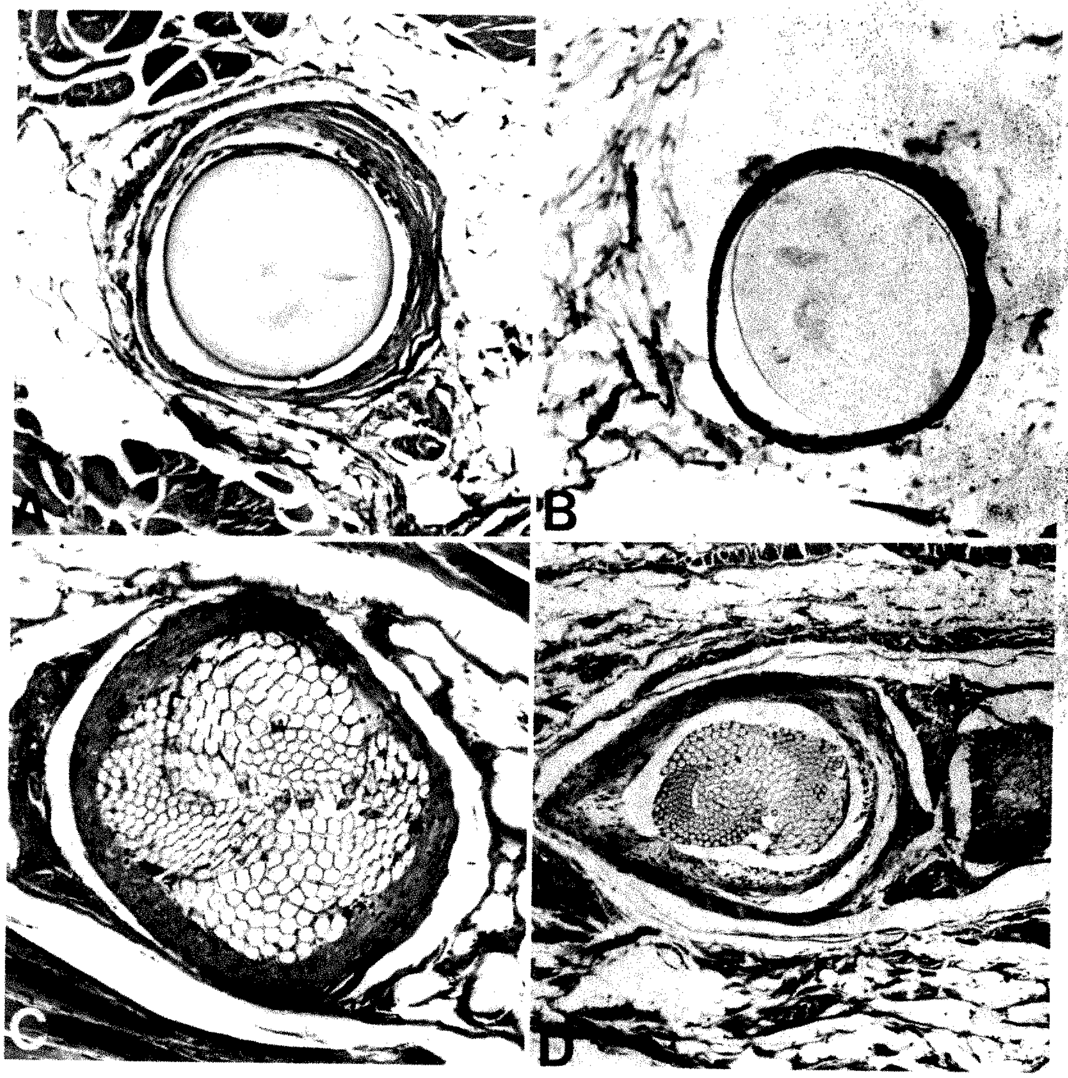


FIG. 1. Nylon in A and polypropylene in B show narrow rim of fibrous tissue. Dacron in C shows slightly more tissue reaction. Teflon has shed off the dacron, in D, and stimulated the reaction in the two triangular areas to the right of the suture (A, B, C × 140; D × 70).

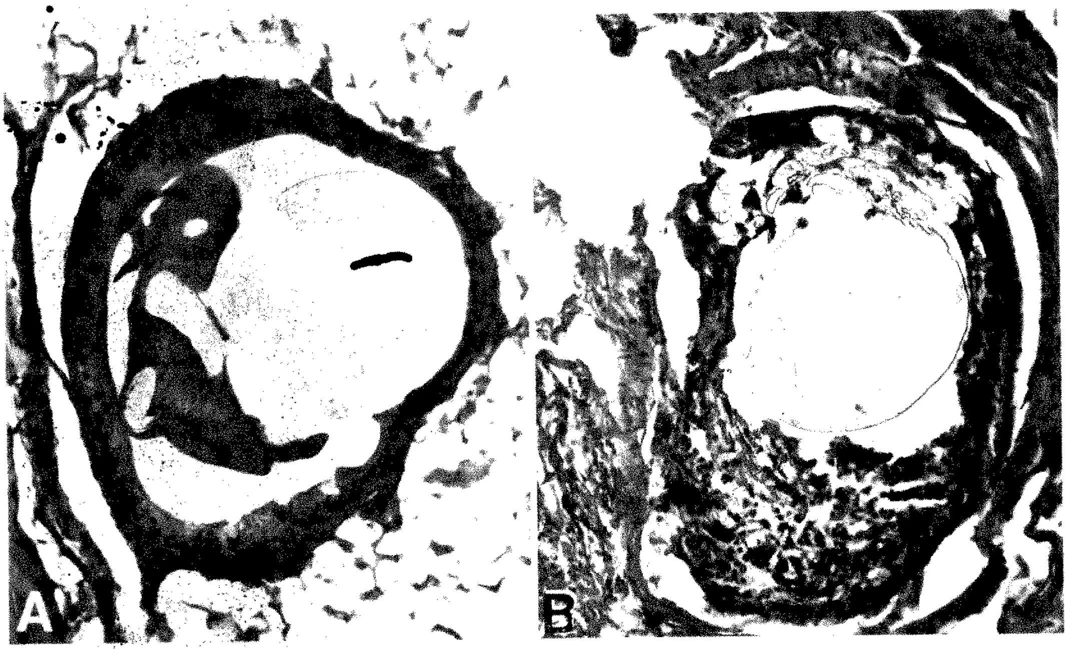


FIG. 2. In A, four comparatively large fragments of polypropylene are shown; three embedded in fibrous tissue. In B, multiple small fragments are seen above the suture (×140).

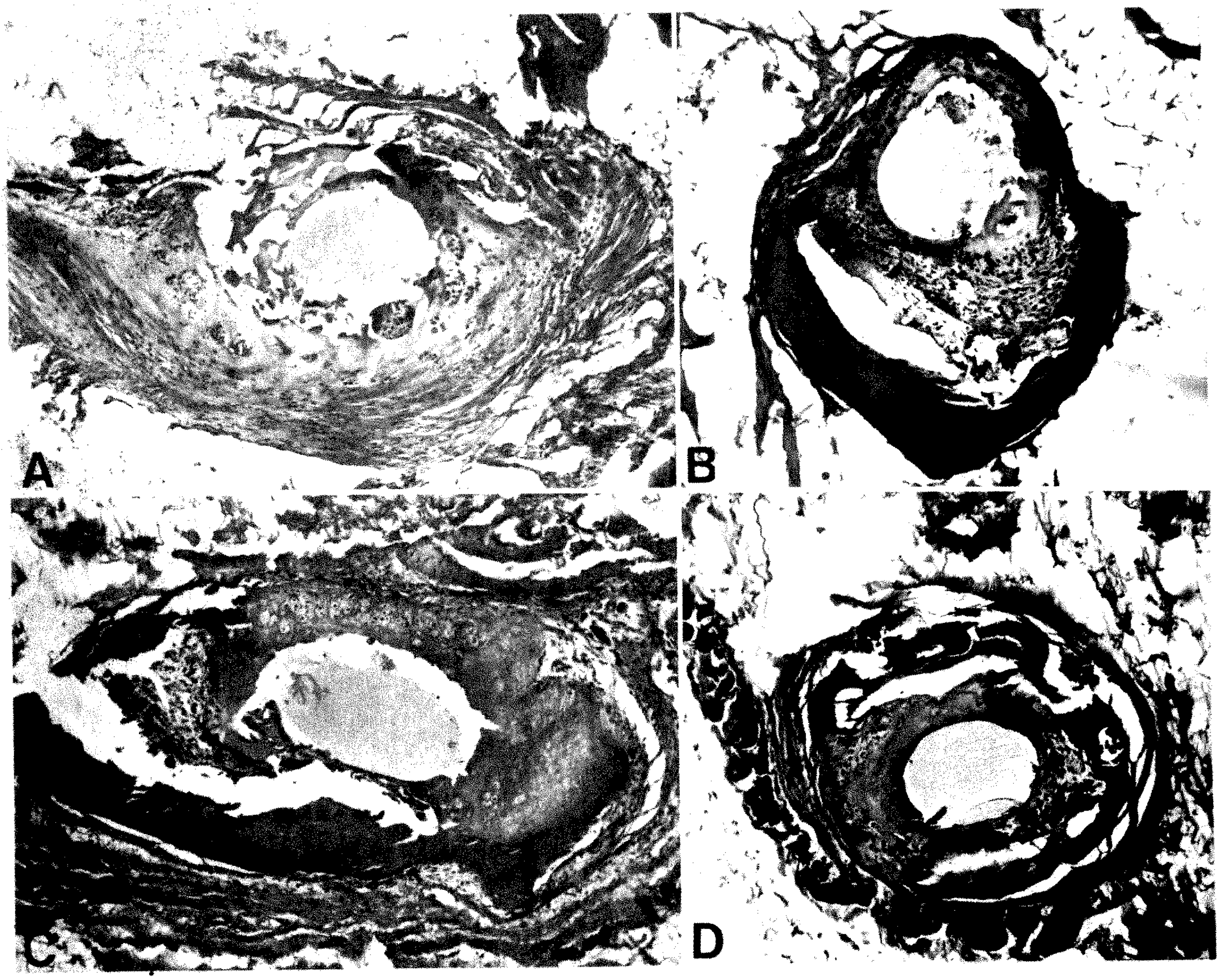


FIG. 3. Four examples of bone and cartilage formation around polypropylene. In addition, fragmentation is seen in A and B (×70).

growth as a cuff of tissue about a suture has been described as far as can be determined.

Also unexplained is the time the changes in or around the polypropylene developed. Divisions into two periods, 6–29 months and 30–60 months, shows 209 polypropylene sutures were examined in the first period and 142 in the second. In the first 29 months, 11 of the 14 instances of fragmentation were found and all of bone–cartilage formation. Conceivably, resorption of the bone and cartilage could have occurred in the older animals. In addition, the association of fragmentation with bone–cartilage formation in 5 of 9 cases of the latter suggests that the same abnormal process, chemical or otherwise, could be responsible for both.

Parenthetically, reexamination of the polypropylene sutures from the two year study showed no bone or cartilage formation.

Although in most operations, these minutiae of tissue reaction concerning polypropylene are of little consequence, it may be necessary to conduct further studies to determine if they have any significance.

References

1. Liebert, T. C., Chartoff, R. P., Cosgrove, S. L., and McCuskey, R.: Subcutaneous Implants of Polypropylene Filaments. J. Biomed. Mater. Res., 10:939, 1976.
2. Postlethwait, R. W.: Long-term Comparative Study of Nonabsorbable Sutures. Ann. Surg., 171:892, 1970.
3. Postlethwait, R. W.: Tissue reaction to surgical sutures. *In* Dunphy, J. E. and VanWinkle, W., Jr. (eds) Repair and Regeneration. McGraw-Hill, New York, Chapter 19, 1969, pp. 263–285.
4. Rhone, D. P. and Horowitz, R. N.: Heterotopic Ossification in the Pulmonary Metastases of Gastric Adenocarcinoma. Report of a Case and Review of the Literature. Cancer, 38: 1773, 1976.

Carcinoid Tumors of the Appendix

Mesoappendiceal Extension and Nodal Metastases

DONALD C. SYRACUSE, M.D., KARL H. PERZIN, M.D., JOHN B. PRICE, M.D., PHILIP D. WIEDEL, M.D.,
RICARDO MESA-TEJADA, M.D.

*From the Departments of Surgery and of Pathology,
Division of Surgical Pathology, Columbia University,
College of Physicians and Surgeons and the Columbia-
Presbyterian Medical Center, New York, New York*

Carcinoid of the appendix occurred in 92 of 400,000 surgical pathology specimens covering 70 years, and followed previously reported incidences by age, sex, symptoms, size, location and histology. Invasion of the mesoappendix occurred in 13 cases, and in two of these, a reoperative ileocolectomy demonstrated regional node metastases. No distant metastases or fatalities appeared. Tumor size correlated with mesoappendiceal invasion. Carcinoid invasion of the mesoappendix may provide a valuable marker for more distant tumor spread, and justify an aggressive surgical approach in selected patients.

CARCINOID OF THE APPENDIX was first described by Merling[11] in 1808 but it was not until 1880 in a report by Ransom[16] that metastases were associated with the tumor. McDonald[9] commented in 1956 that only 13 cases of metastases from an appendiceal carcinoid were adequately confirmed and all involved only regional lymph nodes. Since then several additional reports of metastatic appendiceal carcinoid have appeared. By 1972 Cunningham[2] wrote that of 1,700 reported cases of appendiceal carcinoid, 37 (2%) had metastasized; in 21, the metastases only involved the regional lymph nodes.

We present two additional cases of metastatic appendiceal carcinoid to regional lymph nodes. Both patients underwent a reoperation for removal of possible residual carcinoid when the original specimen on microscopic examination showed mesoappendiceal invasion. A review of our experience with carcinoid of the appendix suggests that invasion of the mesoappendix can be associated with regional node spread and should prompt consideration for a more extensive procedure than simple appendectomy.

Experience

The records of our Surgical Pathology Laboratory contained 92 cases of appendiceal carcinoid tumors examined during the past 70 years. These lesions were found among 196 carcinoid tumors of various sites, which are shown in Table 1. In addition, 14 other carcinoids were identified in the liver, peritoneum or mesentery, their primary sites not having been determined. No ovarian carcinoids were listed since we do not usually receive gynecologic specimens in our laboratory.

The age and sex distribution of our patients can be found in Table 2 and are similar to those reported in other studies.[12,13,15]

Appendiceal carcinoids rarely could be implicated in the pathologic process which led to abdominal exploration. In only seven patients was the tumor possibly related to the clinical problem: six patients had acute appendicitis in the distal tip with a proximally occlusive carcinoid and one patient had a small bowel obstruction with invasion of the ileum from an appendix encased with carcinoid. In 83 patients, the carcinoid was found incidentally and not related to the pathologic process. Of these, 42 patients were explored for acute appendicitis and 41 patients underwent a prophylactic appendectomy associated with: gall bladder disease (21 cases); gynecologic disorders (8); colonic carcinoma (5); regional enteritis (3); ulcerative colitis (1); peptic ulcer (1); adhesions (1); and urinary tract disease (1). In two cases, we could not determine the reason for the operation.

Reprint requests: Donald C. Syracuse, M.D., Department of Surgery, Columbia University, College of Physicians and Surgeons, 630 West 168 Street, New York, New York 10032.

Submitted for publication: January 17, 1979.

0003-4932/79/0700/0058 $00.80 © J. B. Lippincott Company

TABLE 1. *Sites of Origin of 196 Carcinoid Tumors*

Appendix		92
Rectum		45
Small intestine		32
Ileum	23	
Jejunum	4	
Duodenum	5	
Lung		13
Stomach		8
Colon		4
Mediastinum		1
Pancreas		1

The extent of local spread and tumor size are recorded in Table 3. Although penetration of carcinoid to the muscularis and serosa were common, extension to the mesoappendix occurred in only 13 of the 92 cases (14%). The extent of invasion was related to tumor size. When a tumor was described grossly, mesoappendiceal invasion was found in 11 of 43 cases (26%). However, when the carcinoid was identified only microscopically, mesoappendiceal invasion was seen in two of 49 cases (4%). Only four of the 92 carcinoid tumors measured 1.0 cm or more in diameter and in two of these the mesoappendix was involved.

In our series, as in others,[12,15] carcinoids were found most frequently at the tip of the appendix. In 77 of our 92 cases, the position of the carcinoid was known. Sixty tumors involved the distal tip; 12 occurred in the middle third, and four were found at the base of the appendix. In one case, the tumor involved the entire length of the appendix.

Mesoappendiceal invasion occurred with a distribution which reflected the relative incidence of the tumor at each position along the length of the appendix. Of the 13 carcinoids which invaded the mesoappendix, eight originated in the tip, while one each arose from the central and basal portions of the appendix. In three patients, the original site of the tumor could not be determined.

Six patients underwent an ileocolectomy for reasons unrelated to carcinoid, but the specimens contained an incidental appendiceal carcinoid. None of these specimens showed mesoappendiceal invasion and none demonstrated regional node involvement with carcinoid.

One patient who presented with small bowel obstruction underwent an ileocolectomy for an unusually large carcinoid which appeared to arise in the appendix, although an ileal or cecal primary could not be ruled out. The appendiceal mass measured 4 cm in diameter and had produced a cast of the appendix. The mesoappendix, ileum and cecum were infiltrated with carcinoid. However, despite its local aggressiveness, no regional nodes were involved with tumor.

Two patients underwent a reoperative ileocolectomy prompted by the finding of carcinoid infiltration of the mesoappendix. Both patients had regional node metastases and are detailed below.

Case Reports

Case 1. This 48-year-old man underwent an elective cholecystectomy with an incidental appendectomy. The appendix, small bowel, liver and all other intra-abdominal structures were grossly normal. Postoperatively there were no complications. The pathology report described an appendiceal carcinoid at the distal tip measuring 1 cm in diameter with extension into the mesoappendix (Fig. 1). One mesoappendiceal lymph node was found to contain nests of carcinoid in the marginal sinuses (Figs. 2 and 3). Three months later the patient underwent a reoperation with the findings of a healed appendiceal stump and no enlarged nodes. An ileocolectomy and omentectomy were performed with an end-to-end ileotransverse colostomy. The patient recovered uneventfully. The specimen contained 52 lymph nodes, one of which showed nests of carcinoid cells in a marginal sinus. The immediate area adjacent to the stump inversion was free of tumor. Four years later the patient remains well.

Case 2. This 31-year-old woman underwent an uncomplicated, elective cesarean section. During routine abdominal exploration, all structures were normal, except the appendix which had a central thickening and congestion of its serosal surface. An appendectomy was performed with the impression of subacute appendicitis and the patient recovered uneventfully. The pathology report described a carcinoid measuring 1.5 cm in diameter with invasion of mexoappendiceal fat (Fig. 4). The patient was discharged to return in two months for an ileocolectomy. At the time of reoperation, slightly enlarged mesenteric lymph nodes were identified, otherwise the exploration was unremarkable. An ileocolectomy including the mesentery was performed with an end-to-end ileotransverse colostomy. The patient recovered without difficulty. The specimen showed no residual tumor at the appendectomy site, but two of 67 mesenteric lymph nodes had carcinoid in the peripheral sinuses (Fig. 5). Both of the nodes were found distant to the immediate periappendiceal region. The remaining nodes showed reactive hyperplasia. Four years later the patient remains well.

TABLE 2. *Age and Sex Distribution*

	Total	10–19	20–29	30–39	40–49	50–59	60–69	70–79	Unknown
Male	30	2	7	4	6	3	2	6	—
Female	62	9	16	12	9	9	2	1	4
Total	92	11	23	16	15	12	4	7	4

TABLE 3. *Size and Location of Carcinoid Tumors*

	Total	Mucosa or Submucosa	Muscularis	Serosa or Subserosa	Mesoappendix Fat
No tumor recognized or described	49	16	18	13	2
Tumor seen not measured	11	—	2	6	3
1.0 cm or less	28	1	9	12	6*
1.1–1.5 cm	3	—	—	2	1*
1.5 cm or more	1	—	—	—	1
Total	92	17	29	33	13

* Including one case with lymph node metastasis.

Discussion

Controversy continues over the indications for more extensive procedures than simple appendectomy for carcinoid of the appendix. Moertel and associates[12] in an analysis of the world's literature and summary of cases treated at the Mayo Clinic through 1967, concluded that more than a simple appendectomy should be considered only if: 1) grossly metastatic disease were identified, or 2) if the primary carcinoid tumor measured 2 cm or greater in diameter. Pearlman and Srinivasan[14] challenged the 2 cm rule with a case report of an appendiceal carcinoid metastatic to a regional mesenteric lymph node in which the original tumor measured only 1.4 cm in diameter. Dent and coworkers[3] reported two patients with nodal metastases from primary appendiceal carcinoids 1.0 cm in diameter. They concluded that a radical right hemicolectomy is indicated in patients whose tumors measured more than 1 cm in diameter or who had gross evidence of regional lymph node metastasis. We have added two additional cases of metastasizing appendiceal carcinoids measuring 1.0 and 1.5 cm and concur with Dent's recommendations.

Moertel and associates also claimed that simple appendectomy was adequate regardless of the location of the lesion. Ponka and colleagues[15] supported this view, citing a patient who was well 17 years following an appendectomy in which a carcinoid tumor was incompletely excised from the base of the appendix. In contrast, Latham and coworkers[8] and Kantor and associates[6] have argued that involvement of the proximal

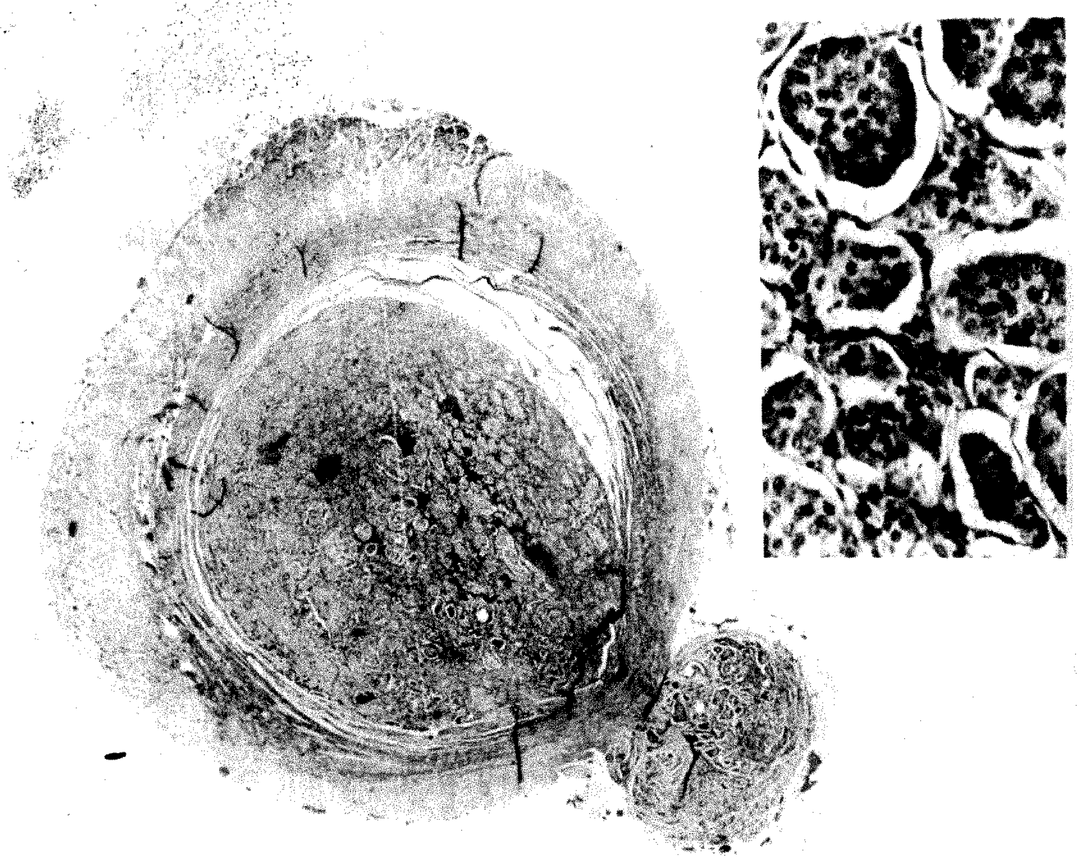


FIG. 1. Case 1. This low power view shows a cross section of the appendix. Tumor has filled the lumen and has replaced the mucosa. On the lower right, the lesion has invaded through the muscularis and has extended into the mesoappendix. The inset in the upper right demonstrates a higher power view of the neoplasm which has the classical features of carcinoid tumor. The lesion produces solid nests of cells with uniform nuclei (C 48279, ×16, inset ×160).

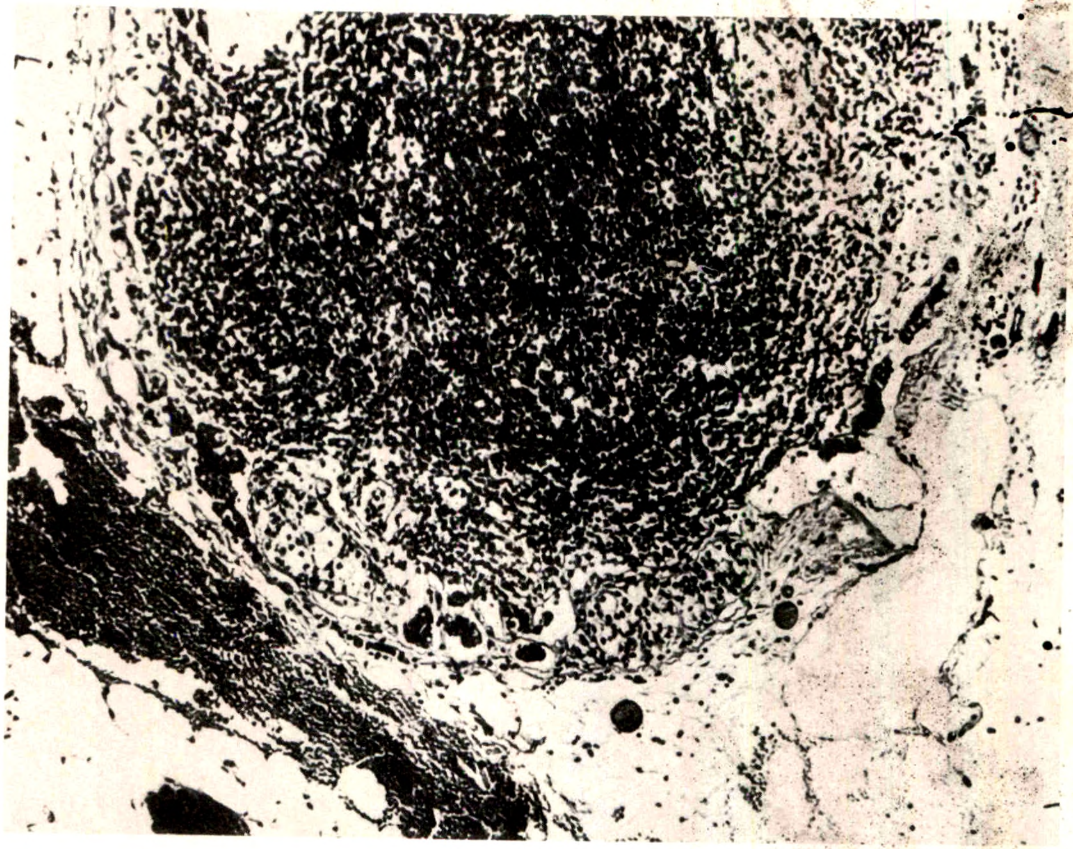


Fig. 2. Case 1. This lymph node which was found in the mesoappendix contains small nests of metastatic carcinoid tumor in a peripheral sinus (C 48279, ×90).

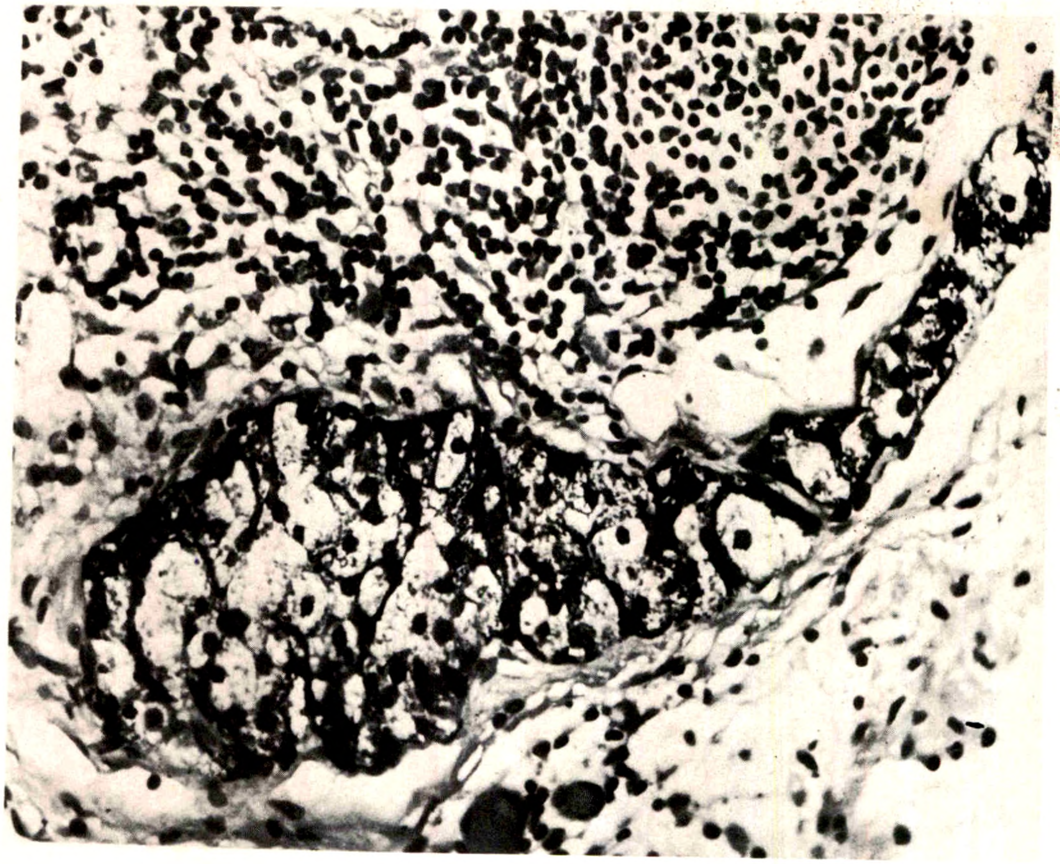


Fig. 3. Case 1. This silver stain shows argentaffin positive black granules in the cytoplasm of tumor cells which are found here in the peripheral sinus of the mesoappendiceal lymph node (C 48279, Long Fontana Silver stain, ×300).

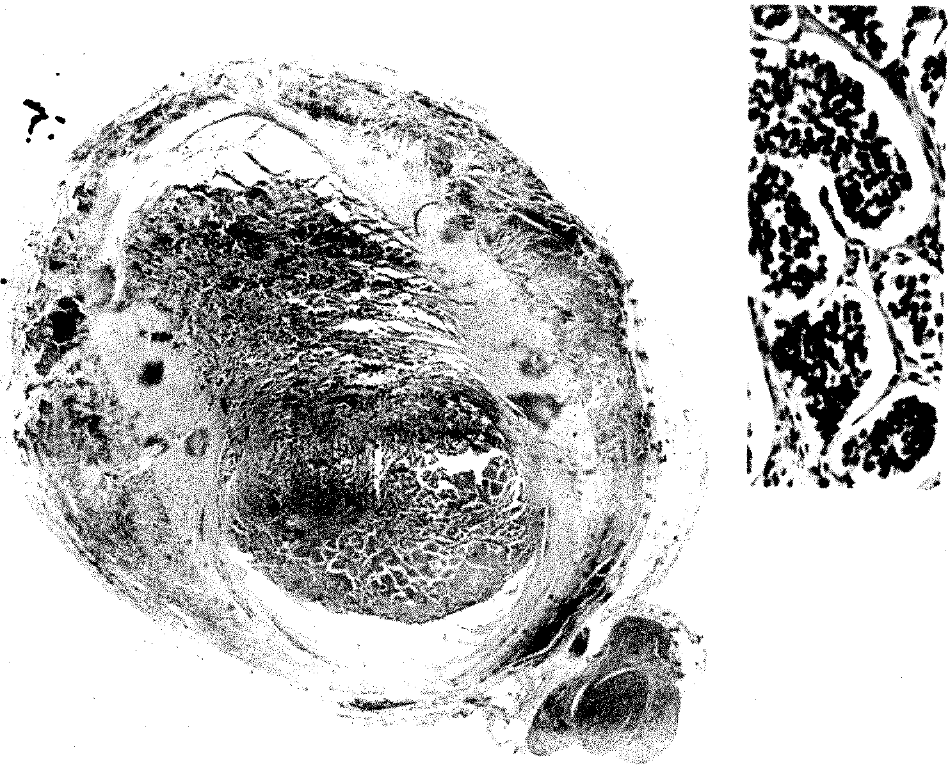


FIG. 4. Case 2.
power view show
section of the
with tumor filling tl
On the left, the l
extended through
cularis to the se
the lower right,
plasm has invaded
appendix. The ins
upper right illus
higher power vie
lesion which dem
the classical fea
carcinoid tumor
×12, inset ×160).

appendix with carcinoid should prompt an ileocolectomy. Neither of our two patients had basal involvement of the appendix. Indeed, of the 13 appendiceal carcinoids which showed mesoappendiceal invasio one arose from the base. Therefore, our data support the importance of the position of origin

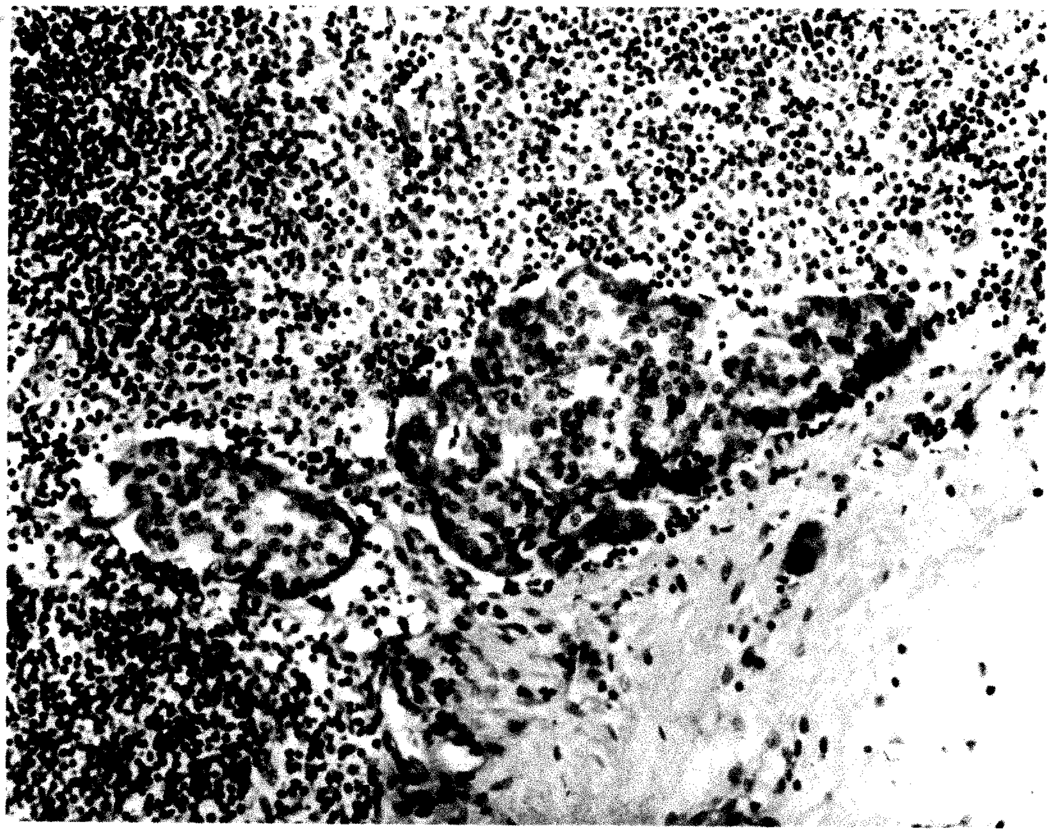


FIG. 5. Case 2. T
cecal mesenteric
node resected with
colectomy contains
tumor cells in a
sinus. Note the
nuclei and the sim
these cells to thos
in Figure 4. (C5244

the appendix as a determinant of the need for more than a simple appendectomy. However, if tumor appears at the line of excision, further resection should be considered.

The strongest challenge to Moertel's findings has evolved over the importance of lymphatic invasion found microscopically. Dent and associates could not confirm the nearly universal lymphatic involvement of appendiceal carcinoid reported by Moertel. When strict criteria of endothelial lined spaces were used to distinguish lymphatics from artifact, Dent and associates found only 5 of 29 cases (17.2%) of appendiceal carcinoids had extension into lymphatics. However, we have found that lymphatic invasion is a difficult histologic criterion. Carcinoid cells tend to cluster and shrink from the supporting stroma making it difficult to decide whether nests of tumor cells are present in stroma or in lymphatic spaces. We consider the finding of any carcinoid cells in the mesoappendix, whether they are located in fat, fibrous tissue or lymphatic spaces, as a possible marker for metastatic disease.

Many questions remain. What is the frequency of positive nodes once carcinoid is found in the mesoappendix? Our series showed positive regional nodes in two patients reoperated upon when carcinoid was found in the mesoappendix. Eleven additional patients with similar mesoappendiceal invasion were found retrospectively, but none underwent reoperation and the state of their regional nodes is unknown.

Can regional nodes be involved without mesoappendiceal invasion? The failure to demonstrate metastatic carcinoid in six patients who underwent an ileocolectomy for reasons unrelated to an incidental carcinoid suggests that regional nodes are not involved when the tumor does not extend to the mesoappendix. Clearly, more patients are required before a generalization can be reached.

What is the natural history of carcinoid if left behind in regional nodes? In our series, no patient had widespread disease from an appendiceal carcinoid. Moreover, in the records of our surgical pathology laboratory, which include more than 400,000 surgical cases (covering 70 years) we have no instance of an appendiceal carcinoid metastatic to sites other than the regional lymph nodes. However, an occasional case of distantly metastatic carcinoid,[1,7,17] including the syndrome,[10] has been reported as arising from the appendix. To date, four patients have succumbed to their tumor.[4] Even in the Mayo Clinic series, two patients who eventually died presented with widespread metastatic disease confirmed at autopsy to arise from an appendiceal carcinoid. Whether an early, extended procedure might have salvaged these patients is conjectural.

The policy we follow emphasizes the presence of tumor invasion to the mesoappendix. Mesoappendiceal invasion may provide the histologic marker of possible nodal spread. Tumor size influences extension to the mesoappendix. In general, carcinoids greater than 1 cm in diameter should be highly suspect for mesoappendiceal invasion, whereas tumors less than 1 cm infrequently will show such extension. In all cases, the mesoappendix should be carefully examined.

Whenever the mesoappendix is involved with tumor, the question arises whether more than a simple appendectomy should be performed. Unfortunately, the definitive data are still unavailable. For each patient, the risks of leaving tumor behind must be weighed against the risks of an elective ileocolectomy. In an otherwise healthy patient who can look forward to a long life span, our current policy is to perform an ileocolectomy when the mesoappendix is invaded by carcinoid. This policy seems particularly appropriate when a mesoappendiceal lymph node is infiltrated with tumor. We suggest that involvement of the mesoappendix may prove a valuable marker for regional node spread and justify our aggressive surgical approach.

References

1. Campanale, R. P. and Prothero, S. R.: Malignant Appendiceal Carcinoid (Argentaffinoma) with Regional Lymph Node Metastasis. Am. J. Surg., 107:855, 1964.
2. Cunningham, P. J., Norman, J. and Cleveland, B. R.: Malignant Carcinoid Associated with Thoraco-Abdominal Aneurysm and Analysis of 31 Cases of Gastrointestinal Carcinoid Tumors. Ann. Surg., 176:613, 1972.
3. Dent, T. L., Batsakis, J. G. and Lindenauer, S. M.: Carcinoid Tumors of the Appendix. Surgery, 73:828, 1973.
4. Godwin, J. D., II: Carcinoid Tumors: An Analysis of 2837 Cases. Cancer, 36:560, 1974.
5. Hopping, R. A., Dockerty, M. B. and Masson, J. C.: Carcinoid Tumor of the Appendix. Report of a Case in which Extensive Intra-abdominal Metastases Occurred. Arch. Surg., 45:613, 1942.
6. Kantor, S., Crane, R. D. and Gillesby, W. J.: Carcinoid Tumors of the Gastrointestinal Tract. Am. Surg., 27:448, 1961.
7. Kieraldo, J., Eversole, S. and Allen, R.: Carcinoid Tumor of the Vermiform Appendix with Distant Metastasis. Calif. Med., 99:161, 1963.
8. Latham, W. D., Arnold, H. S. and Ede, S.: Kultschitzky-Cell Carcinoma (Carcinoid) of the Appendix with Metastasis. Am. J. Surg., 102:607, 1961.
9. MacDonald, R. A.: A study of 356 Carcinoids of the Gastrointestinal Tract. Am. J. Med., 56:867, 1956.
10. Markgraf, W. H. and Dun, T. M.: Appendiceal Carcinoid with Carcinoid Syndrome. Am. J. Surg., 107:730, 1964.
11. Merling: Cited by Forbus, W. D.: Argentaffin Tumors of the Appendix and Small Intestine. Bull. Johns Hopkins Hosp., 37:130, 1925.
12. Moertel, C. G., Dockerty, M. B. and Judd, E. S.: Carcinoid Tumors of the Vermiform Appendix. Cancer, 21:270, 1968.
13. Morgan, J. G., Marks, C. and Hearn, D.: Carcinoid Tumors of the Gastrointestinal Tract. Ann. Surg., 180:720, 1974.
14. Pearlman, D. M. and Srinivasan, K.: Malignant Carcinoid of the Appendix. N.Y. State J. Med., 71:1529, 1971.
15. Ponka, J. L.: Carcinoid Tumors of the Appendix: Report of Thirty-Five Cases. Am. J. Surg., 126:77, 1973.
16. Ranson, W. B.: A Case of Primary Carcinoma of the Ileum. Lancet, 2:1120, 1890.
17. Turner, M. Gallager, H. S.: Occult Appendiceal Carcinoid. Report of a Case with Fatal Metastases. Arch. Pathol., 88:188, 1969.

The Undescended "Parathymus"

An Occasional Cause of Failed Neck Exploration for Hyperparathyroidism

ANTHONY J. EDIS, M.D., DON C. PURNELL, M.D., JONATHAN A. VAN HEERDEN, M.B., F.R.C.S(C)

From the Mayo Clinic and Mayo Foundation,
Rochester, Minnesota

Arrested descent of the inferior parathyroid gland ("parathymus") during embryologic development may leave the gland stranded high in the neck. Adenomas of such undescended glands are a rare cause of primary hyperparathyroidism, but they may not be uncommon among patients who have already had a failed cervical exploration. Unless the surgeon is aware of this entity, he will probably overlook it. If one is to find these tumors, it is necessary to extend the dissection upward above the superior pole of the thyroid gland, sometimes as far as the angle of the jaw. Adenomas of undescended "parathymus" glands were encountered in seven patients during a recent 20 month (May 1975 through December 1976) surgical experience encompassing 414 primary operations and 27 reoperations for hyperparathyroidism. These tumors were found at initial exploration in one patient and at reoperation in six patients. The individual case histories are presented to illustrate the difficulties posed by this anatomic variant.

SUCH IS THE PROXIMITY of the inferior parathyroid gland to the thymus during embryologic development that Weller[9] called it the "parathymus" gland (Fig. 1). This is a useful descriptive term because it serves to remind the surgeon that, in almost half the patients undergoing cervical exploration for hyperparathyroidism, an inferior parathyroid will be found within the thymic tongue at the thoracic inlet.[7] Similarly, one can readily appreciate how the inferior parathyroid might occasionally overshoot its usual adult location during caudal descent and end up with the thymus in the mediastinum. About 1–2% of patients with primary hyperparathyroidism will be found to have an adenoma arising in one of these ectopic mediastinal "parathymus" glands.[4,6]

Arrested descent of the third branchial pouch complex may also occur and leave the inferior parathyroid stranded high in the neck. Sometimes, a small amount of thymus is still attached to this undescended gland, and this serves to identify the latter as "parathymus." This phenomenon occurs infrequently: in a recent anatomic study of normal parathyroid glands in postmortem subjects, Wang[7] found only three of 312 inferior parathyroid glands in an undescended location.

This report describes seven patients with primary hyperparathyroidism due to adenomas of undescended "parathymus" glands. Six of these tumors were overlooked at initial cervical exploration and were ultimately found at reoperation by extending the dissection into the zone above the superior pole of the thyroid. Our belated recognition of this unusual anatomic variant finally permitted expeditious identification and removal of an undescended "parathymus" adenoma in a seventh patient at primary operation.

Our purpose in reporting these cases is to acquaint those interested in parathyroid surgery with this problem. To our knowledge, only one other case has been previously described,[8] and it is doubtful that many surgeons recognize the existence of the phenomenon.

Case Reports

Case 1. In August 1973, this 20-year-old man underwent cervical exploration (elsewhere) for primary hyperparathyroidism complicated by nephrolithiasis. An adenoma of the left superior parathyroid gland weighing 2.2 g was removed, and a normal right inferior parathyroid gland was also excised. Neither of the two remaining glands was identified. The patient remained hypercalcemic postoperatively. His subsequent clinical course was complicated by the necessity for left ureterolithotomy in November 1974.

He was first seen at the Mayo Clinic in May 1975, at which time the serum level of calcium was 12.1 mg/dl (normal range 8.9–10.1 mg/dl) and the serum concentration of immunoreactive parathyroid

---

Reprint requests: Anthony J. Edis, M.D., Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901.

Submitted for publication: January 22, 1979.

0003-4932/79/0700/0064 $00.75 © J. B. Lippincott Company

hormone (iPTH)* was 75 μleq/ml (normal <45 μleq/ml). Roentgenograms of the hand showed evidence of subperiosteal resorption; no kidney stones were present at this time. Re-exploration of the neck was advised.

At operation, a normal right superior parathyroid gland was identified and biopsied. We expected to find the missing left inferior parathyroid gland in the lower left region of the neck or the superior mediastinum, but a careful search of these areas was unrewarding. Ultimately, the tumor was found high on the left side of the neck at the level of the superior cornu of the thyroid cartilage and partially retropharyngeal (Fig. 2). It was an adenoma of the undescended left inferior parathyroid gland, weighing 1,135 mg.

Postoperatively, the serum level of calcium decreased promptly into the normal range, and the patient has remained normocalcemic since.

Case 2. This female patient was first found to have kidney stones and hypercalcemia at the age of 15 years in February 1974. She was hospitalized at that time with pyelonephritis. Cervical exploration was carried out soon after, and the left superior parathyroid gland was removed; two other glands were biopsied. Despite a careful review of the operative record, it was quite impossible to determine which glands had been biopsied. The histologic features of all three glands were reviewed and described as normal. Hypercalcemia persisted postoperatively.

The patient was first evaluated at the Mayo Clinic in March 1975. The serum level of calcium was 11.1 mg/dl, and the serum level of iPTH was 52 μleq/ml. We could find no evidence of bone disease; two calculi were present in the upper and middle pole calyces of the right kidney. A parathyroid arteriogram (Fig. 3) was performed which clearly demonstrated a vascular mass, 1.4 × 2.4 cm, in the upper region of the neck on the right. The tumor was situated well above the superior pole of the thyroid and slightly to the right of midline. A selective venous sampling study was also carried out. The peripheral venous level of iPTH† in the inferior vena cava was 0.39 ng/ml. An increase in concentration of parathyroid hormone to 2 ng/ml was detected in the right inferior thyroid vein which lateralized a hyperfunctioning gland to this side.

Cervical re-exploration was carried out in May 1975, and a parathyroid adenoma was removed from the retropharyngeal position above the right superior pole of the thyroid (Fig. 2). It weighed 510 mg. Interestingly, a lobule of thymus was attached to the adenoma, and this identified it with certainty as an undescended "parathymus."

Postoperatively, the serum level of calcium returned to normal.

Case 3. In the course of evaluation for hypertension in 1968, this female patient was found to have nephrocalcinosis and an elevated serum level of calcium. She was 37 years of age at that time. Cervical exploration was carried out at the Mayo Clinic in January 1968, and a normal right superior parathyroid gland was removed. The right inferior parathyroid gland was identified grossly. A single normal parathyroid was identified on the left side which was described as the inferior gland, but its specific anatomic location was not described.

Hypercalcemia persisted postoperatively, and the neck was re-explored in April 1968. Again, no tumor was found. A subsequent thyrocervical arteriogram was carried out in an attempt to localize the missing tumor, but none was identified. The patient was started on treatment with oral phosphate. In March 1972, the patient underwent combined exploration of the neck and mediastinum, for which a sternal split was employed. No tumor was found. In December 1975, the serum level of calcium was 13.4 mg/dl and that of iPTH was 180 μleq/ml. Hand x-ray films revealed subperiosteal resorption, and bilateral nephrocalcinosis was again documented. In the same month, a fourth exploration of the neck was carried out and a bilateral subtotal thyroidectomy was performed. This time, no parathyroid tissue whatsoever was encountered. The patient continued on treatment with oral phosphate, but she did not do well and complained of persistent malaise, fatigue, nausea, recurrent joint stiffness, headaches, and depression. A thyrocervical and internal mammary arteriogram was carried out and was negative for tumor. A computerized tomogram of the mediastinum and neck was likewise unrevealing. A selective venous sampling study was performed, and an increase in concentration of hormone of 5.3 ng/ml was found in a so-called right paravertebral vein (compared with a peripheral level of 1.5 ng/ml). On the basis of this finding, a fifth exploration of the neck was carried out, in September 1976. A radical neck dissection was performed, with transection of the internal jugular vein on the right. Only then was the tumor found, situated about 2 cm above the carotid bulb (Fig. 2). It measured about 3 cm in diameter and weighed 2,575 mg.

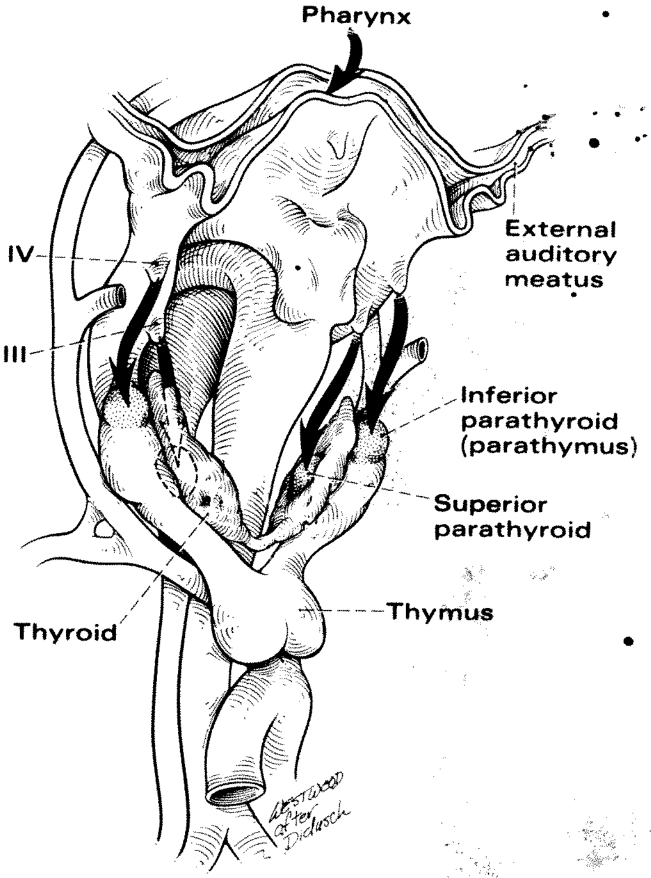


FIG. 1. Inferior parathyroid gland and thymus have a common embryologic origin from third branchial pouch and are closely related during caudal descent—hence the term "parathymus." Arrested descent results in undescended "parathymus." Superior parathyroid gland arises from fourth pouch and is thereafter more closely associated with thyroid.

---

* Antibody with predominantly carboxyl terminal recognition capability.

† Antibody with predominantly amino terminal recognition capability.

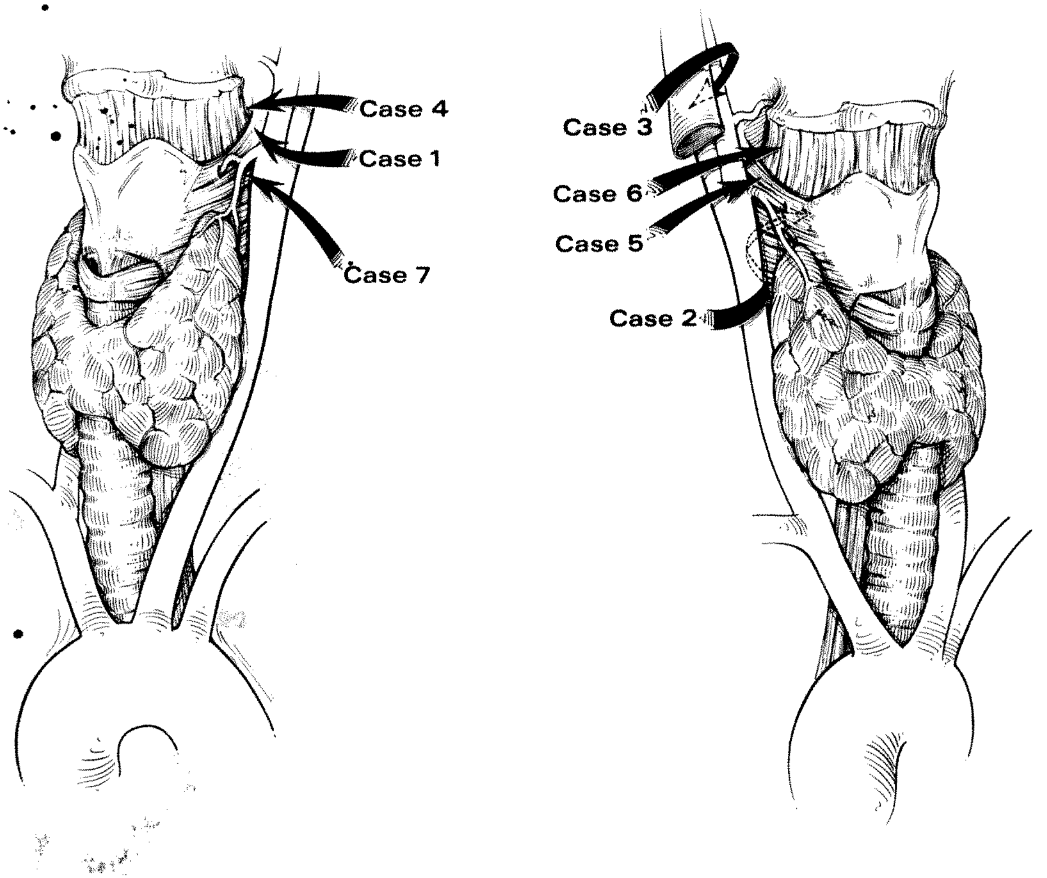


FIG. 2. Locations of adenomas of undescended "parathymus" glands in seven patients.

Postoperatively, the patient became hypocalcemic and required treatment with supplemental calcium carbonate by mouth. She has since remained well and has been eucalcemic on calcium therapy.

Case 4. This 58-year-old woman was referred to the Mayo Clinic in September 1974 for evaluation and treatment of a severe demineralizing bone disease that caused pain in the lower extremities and hips. She had suffered progressive bowing of the legs affecting the femora primarily and creating the necessity for a suprapatellar osteotomy on the left side. A spontaneous fracture of the left femur occurred in April 1974. There was no specific radiologic evidence for osteitis fibrosa cystica, but a bone biopsy showed increased osteoblastic and osteoclastic activity and intertrabecular fibrosis consistent with hyperparathyroidism. The serum concentration of calcium was 12.9 mg/dl and that of iPTH was 68 μleq/ml. Cervical exploration was advised and carried out that same month.

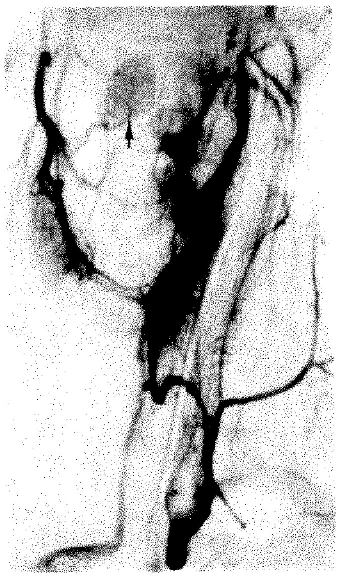


FIG. 3. Selective left superior thyroidal arteriogram in Case 2 shows stain produced by adenoma of undescended "parathymus" (*arrow*). Tumor was located superior to upper pole of thyroid on right and was associated with small remnant of thymus.

Both superior parathyroid glands were identified by biopsy and were normal. Neither inferior gland was found. Hypercalcemia persisted postoperatively. In November 1974, a formal mediastinal exploration was carried out via median sternotomy, but no parathyroid tissue was identified. In February 1975, a parathyroid arteriogram was performed but failed to show a parathyroid tumor. The next month, a selective venous sampling study was performed. There was no significant increase in hormone concentration in the small thyroid veins. In the meantime, the patient was treated with oral phosphate to control her hypercalcemia, but the medication caused considerable nausea. Ultimately, re-exploration of the neck was undertaken, in November 1975.

This time, the dissection was carried upward into the neck to the level of the hyoid bone, initially on the right side, without finding tissue, and then on the left. High on the left side, just below the level of the hyoid bone and lateral to the superior cornu of the thyroid cartilage (Fig. 2), a 1 cm parathyroid adenoma weighing 550 mg was found and removed.

Postoperatively, the serum level of calcium became stable in the normal range.

Case 5. This female patient was initially referred to us at age 66 in September 1974. Her local physician had detected hypercalcemia in the course of a general medical examination. Studies here revealed a serum level of calcium of 12.8 mg/dl, with a serum level of iPTH of 560 μleq/ml. Hand x-ray films showed subperiosteal resorption, and an excretory urogram demonstrated bilateral renal calculi. A neck scar was present from a previous thyroidectomy for toxic adenomatous goiter performed 15 years previously.

Cervical exploration was undertaken in October 1974, at which time both the left superior and the right superior parathyroid glands were identified and excised. Each weighed 60 mg and histologically was described as showing minimal hyperplasia. Neither inferior gland was identified. Hypercalcemia persisted postoperatively.

In November 1974, a formal mediastinal exploration was carried out via median sternotomy. No parathyroid tissue was identified. The patient was subsequently treated with oral phosphate to maintain the serum level of calcium below 11 mg/dl. In March 1975, a thyrocervical and internal mammary arteriogram was carried out, but no tumor blush was seen. In July 1975, a selective venous sampling study was performed. This demonstrated a pronounced increase in hormone concentration in the right superior thyroid vein of 50 ng/ml, compared with a background level of 2.7 ng/ml. On the basis of this finding, reexploration of the neck was performed in October 1975.

High in the right parapharyngeal area, alongside the superior cornu of the thyroid cartilage (Fig. 2), a 5.96 g parathyroid adenoma was found and removed.

Postoperatively, the serum level of calcium decreased promptly into the normal range, and the patient has remained normocalcemic.

Case 6. This 59-year-old woman was first found to have hypercalcemia in April 1975. She had previously had a right thyroid lobectomy for a benign nodule in 1953 and also a right nephrectomy for suspected ureteral malignancy in 1973; a ureteric calculus had been found. Neck exploration for hyperparathyroidism was undertaken in March 1975, and normal left superior and left inferior parathyroid glands were removed. The patient remained hypercalcemic postoperatively and was subsequently referred to the Mayo Clinic for further evaluation and treatment.

At that time, the serum level of calcium was 11.2 mg/dl and that of iPTH was 180 μleq/ml. A 1 cm nodule was palpable high in the right side of the neck adjacent to the thyroid cartilage. Permission for a parathyroid arteriogram was refused, but the patient agreed to undergo a selective venous sampling study. This demonstrated a significant increase in concentration of hormone in the right superior parathyroid vein (19.2 ng/ml compared with a peripheral level of 1.2 ng/ml)

Re-exploration of the neck was carried out in January 1976. A normal parathyroid gland (presumably the superior gland) was identified lying alongside a nubbin of residual thyroid tissue on the right. Well above this, and corresponding to the nodule that was palpable clinically, the surgeon found a 1 cm parathyroid adenoma weighing 650 mg (Fig. 2).

Postoperatively, the serum concentration of calcium decreased to normal levels, and the patient has remained normocalcemic.

Case 7. This 33-year-old woman was found to be hypercalcemic on routine biochemical screening at the time of a general medical examination. She was asymptomatic, and we could find no evidence of stone or bone disease. The serum level of calcium was 10.8 mg/dl and that of iPTH was 72 μleq/ml.

Cervical exploration was carried out in December 1976. Both the right superior and the left superior parathyroid glands were found in their usual positions and were of normal size and shape. The right inferior gland was also situated in the usual position and was normal. Dissection of the left inferior region of the neck and upper mediastinum was unrevealing. Therefore, we turned our attention to the left upper region of the neck, looking for an undescended "parathymus," and we found a parathyroid adenoma weighing 760 mg above the superior pole of the thyroid in a parapharyngeal position (Fig. 2).

Postoperatively, the serum level of calcium became stable in the normal range.

Discussion

The first six cases illustrate the problems engendered when the surgeon fails to recognize the presence of an adenoma in an undescended "parathymus." In patient 7, we were able to apply the lessons learned from our previous experience and, thereby, to find the missing tumor at the first operation without much trouble. An adenoma of an undescended inferior parathyroid gland was suspected when the left inferior gland was not found in its usual position at the base of the neck. Exploration of the upper region of the neck, above the superior pole of the thyroid, revealed the missing tumor.

How common is an adenoma of an undescended "parathymus"? During the 20 month period in which these seven cases were encountered, a total of 414 patients underwent operation for primary hyperparathyroidism at the Mayo Clinic—giving an overall frequency for undescended adenoma of 1.7%. It is perhaps more relevant, however, that six of these patients were discovered among 27 individuals undergoing reoperation for persistent or recurrent hyperparathyroidism. In this special subgroup of patients, the frequency of an undescended parathyroid adenoma was a disconcerting 22.2%. Of course, this figure is probably somewhat inflated, reflecting the concentration of cases occurring at the time we first recognized this entity. Nevertheless, it is our belief that these aberrantly located tumors account for a significant proportion of the missing tumors in patients who have had a failed cervical exploration for hyperparathyroidism. If one or other inferior parathyroid gland has not been identified at the initial operation, and the surgeon has made no effort to explore the zone above the upper pole of the thyroid, an undescended "parathymus" adenoma should be suspected.

Both Cope[1] and Hellström[5] have pointed out that the term "parathyroid" is itself probably one reason why the uninitiated surgeon often explores no more than the region in the immediate vicinity of the thyroid. In this sense, use of the term "parathymus" may serve as a useful reminder to explore the wider area wherein normal and pathologic parathyroids may be located—that is, the zone bounded laterally by and including the thyroid sheath and extending superiorly to the upper border of the larynx and inferiorly as far into the mediastinum as can be carefully dissected from the cervical incision.[2] Also, it is imperative that the radiologist carefully examine the upper region of the neck when performing a thyrocervical arteriogram in patients coming to reoperation. Interestingly, selective venous sampling studies were quite helpful in this special group of patients. In fact, among our reoperative patients, these were the only individuals in whom the study was helpful.[3] Perhaps this is because the upper region of the neck was not dissected at the initial operation and thus distortion of the normal venous anatomy was avoided.

References

1. Cope, O.: Surgery of Hyperparathyroidism: The Occurrence of Parathyroids in the Anterior Mediastinum and the Division of the Operation Into Two Stages. Ann. Surg., 114:706, 1941.
2. Edis, A. J.: Surgical Anatomy and Technique of Neck Exploration for Primary Hyperparathyroidism. Surg. Clin. North Am., 57:495, 1977.
3. Edis, A. J., Sheedy, P. F., II, Beahrs, O. H. and van Heerden, J. A.: Results of Reoperation for Hyperparathyroidism, With Evaluation of Preoperative Localization Studies. Surgery 84:384, 1978.
4. Goldman, L., Gordan, G. S. and Roof, B. S.: The Parathyroids: Progress, Problems and Practice. Curr. Probl. Surg., August 1971, pp. 1–64.
5. Hellström, J.: The Causes of Unsuccessful or Inadequate Parathyroidectomy in Hyperparathyroidism. Acta Chir. Scand., 112:79, 1957.
6. Scholz, D. A., Purnell, D. C., Woolner, L. B. and Clagett, O. T.: Mediastinal Hyperfunctioning Parathyroid Tumors: Review of 14 Cases. Ann. Surg., 178:173, 1973.
7. Wang, C.-A.: The Anatomic Basis of Parathyroid Surgery. Ann. Surg., 183:271, 1976.
8. Wang, C.-A.: Parathyroid Re-exploration: A Clinical and Pathological Study of 112 Cases. Ann. Surg., 186:140, 1977.
9. Weller, G. L., Jr.: Development of the thyroid, parathyroid and thymus glands in man. *In* Contributions to Embryology, No. 141. Vol. 24. Baltimore, Carnegie Institution of Washington, 1932, pp. 95–139.

B[illegible]u[illegible] you need to know which patient is at risk of postoperative thrombosis...

ORTHO* Chromogenic Antithrombin III Assay

Available now for incorporation into your routine screening procedures, as:

- A presurgical screen for levels of Antithrombin III
- An adjunct to heparin monitoring procedures

ORTHO DIAGNOSTICS INC.
Raritan, New Jersey 08869

*Trademark © O.D. 1979

I am interested in Antithrombin III (AT III). Please send me:

☐ Selected reprints on the diagnostic utility of ORTHO* Chromogenic Antithrombin III Assay

☐ An informative brochure on AT III as an inhibitor and the principles of the ORTHO Chromogenic AT III Assay

Name__________

Address__________

City__________ State__________ Zip__________

Your specialty__________

Who, in your hospital, establishes routine presurgical screening procedures__________

*Trademark

ORTHO

Fifth Edition

Rhoads
TEXTBOOK OF
SURGERY
Principles and Practice

●

Edited by JAMES D. HARDY, M.D.
with 279 contributors

Although technically a Fifth Edition of *Surgery: Principles and Practice*, this revision is new in *title, editor, contributing authors, content, approach, and format.* It has been reorganized into three major parts: General Principles of Surgical Practice; Specific Lesions and Dysfunctions Involving Various Organs; and Parasurgical Considerations.

The approach is now problem-oriented and this outstanding volume considers virtually all current problems in surgery.

More than 270 contributors give you an enormous geographical and philosophical range in one volume. Each is well known in his field and discusses management of a specific problem. Included in each of the hundreds of topics discussed are basic features of the operation including a table of basic facts; an overview of the concept under discussion; description of specific pathological conditions; surgical history; physiology; a pathophysiological diagram and an anatomical sketch whenever feasible; many excellent illustrations of disease processes and treatment procedures; possible technical errors; safeguards; postoperative problems; and complications.

2354 Pages / 1738 Illustrations / 313 Tables
5th Edition, 1977 / One Volume Format: $38.50
Two Volume Format: $45.00

Now Available in Either One or Two Volume Form!

Lippincott

J. B. LIPPINCOTT COMPANY
East Washington Square ● Phila., Pa. 19105

In Canada: J. B. Lippincott Company of Canada Ltd.
75 Horner Avenue, Toronto, Ontario M8Z 4X7

Please send me:
Rhoads TEXTBOOK OF SURGERY
☐ 1 Vol. $38.50 ☐ 2 Vols. $45.00

Name ______________________

Address ______________________

City ____________ State ________ Zip ________

☐ Payment enclosed (Save postage and handling)
☐ Charge and bill me (Plus postage and handling)

Also available at your medical bookstore. AS 7/79

M.V.I.® (Multi-Vitamin Infusion)

Each 10 cc. ampul† or 5 cc. Concentrate vial†† provides:

Ascorbic acid (C)	500 mg.
Vitamin A*	10,000 I.U.
Vitamin D* (ergocalciferol)	1,000 I.U.
Thiamine HCl (B_1)	50 mg.
Riboflavin (B_2)**	10 mg.
Pyridoxine HCl (B_6)	15 mg.
Niacinamide	100 mg.
Dexpanthenol	25 mg.
Vitamin E* (dl-alpha tocopheryl acetate)	5 I.U.

†With sorethytan laurate 1%, sodium hydroxide 1%, butylated hydroxytoluene 0.003%, butylated hydroxyanisole 0.0008%; and gentisic acid ethanolamide 2% as preservative.

††With propylene glycol 30% and gentisic acid ethanolamide 2% as stabilizers and preservatives, sodium hydroxide for pH adjustment, sorethytan laurate 1.6%, butylated hydroxytoluene 0.006%, butylated hydroxyanisole 0.0015%.

*Oil-soluble vitamins A, D and E water solubilized with sorethytan laurate.

**In Concentrate as riboflavin-5-phosphate.

BRIEF SUMMARY

INDICATIONS: *in emergency feedings*– Surgery, extensive burns, fractures and other trauma, severe infectious diseases, comatose states, etc. may provoke a "stress" situation with profound alterations in the body's metabolic demands and consequent tissue depletion of nutrients. As a result, wound healing may be impaired, enzyme activity disturbed, hematopoietic tissues affected; hypoproteinemia and edema may appear; convalescence is thus prolonged.

In such patients M.V.I. (administered in intravenous fluids under proper dilution) contributes optimum vitamin intake toward maintaining the body's normal resistance and repair processes.

DIRECTIONS FOR USE: M.V.I. is ready for immediate use when added to intravenous infusion fluids.

For intravenous feeding, one daily dose of 10 cc. of M.V.I. or 5 cc. of M.V.I. Concentrate added directly to not less than 500 cc., preferably 1,000 cc., of intravenous dextrose, saline or similar infusion solutions...plasma, protein hydrolysates, etc.

PRECAUTION: Allergic reaction has been known to occur following intravenous administration of solutions containing thiamine.

CAUTION: Not to be given as a direct undiluted intravenous injection as it may give rise to dizziness, faintness, etc.

THERAPEUTIC NOTE: Intravenous use should be discontinued as early as practical in favor of an intramuscular or oral vitamin preparation, if deemed advisable.

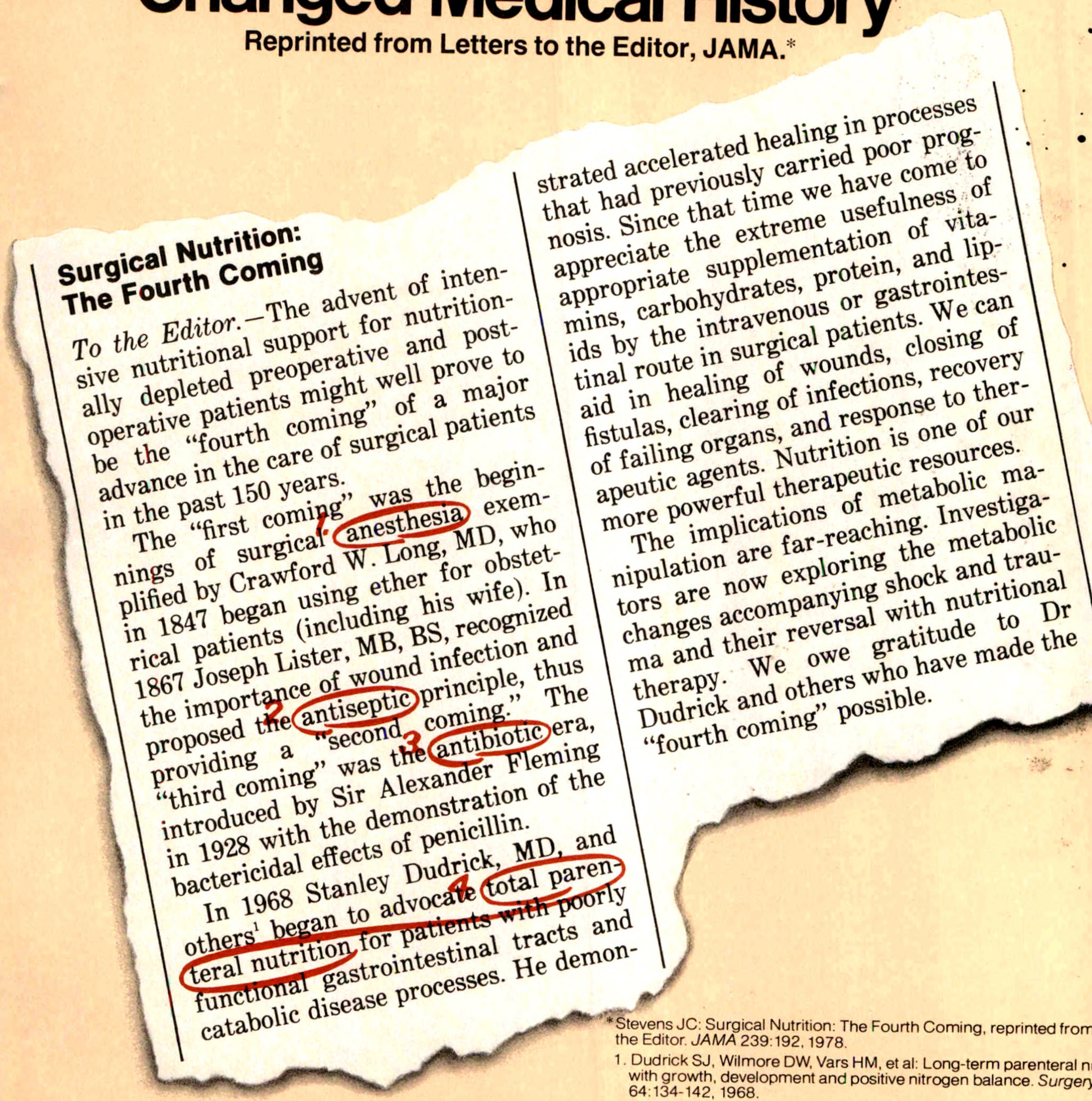
HOW SUPPLIED: M.V.I.–10 cc. ampuls, boxes of 25 and 100 (NSN 6505-00-455-9955/NSN 6505-00-424-9808A).

M.V.I. CONCENTRATE–5 cc. vials, boxes of 25. Available in 100s only (NSN 6505-00-212-6156A).

USV LABORATORIES
USV Laboratories, Division
USV Pharmaceutical Corp.
Tuckahoe, New York 10707

Four Discoveries That Changed Medical History

Reprinted from Letters to the Editor, JAMA.*



Surgical Nutrition: The Fourth Coming

To the Editor.—The advent of intensive nutritional support for nutritionally depleted preoperative and postoperative patients might well prove to be the "fourth coming" of a major advance in the care of surgical patients in the past 150 years.

The "first coming" was the beginnings of surgical 1. anesthesia exemplified by Crawford W. Long, MD, who in 1847 began using ether for obstetrical patients (including his wife). In 1867 Joseph Lister, MB, BS, recognized the importance of wound infection and proposed the 2 antiseptic principle, thus providing a "second coming." The "third coming" was the 3 antibiotic era, introduced by Sir Alexander Fleming in 1928 with the demonstration of the bactericidal effects of penicillin.

In 1968 Stanley Dudrick, MD, and others[1] began to advocate 4 total parenteral nutrition for patients with poorly functional gastrointestinal tracts and catabolic disease processes. He demonstrated accelerated healing in processes that had previously carried poor prognosis. Since that time we have come to appreciate the extreme usefulness of appropriate supplementation of vitamins, carbohydrates, protein, and lipids by the intravenous or gastrointestinal route in surgical patients. We can aid in healing of wounds, closing of fistulas, clearing of infections, recovery of failing organs, and response to therapeutic agents. Nutrition is one of our more powerful therapeutic resources.

The implications of metabolic manipulation are far-reaching. Investigators are now exploring the metabolic changes accompanying shock and trauma and their reversal with nutritional therapy. We owe gratitude to Dr Dudrick and others who have made the "fourth coming" possible.

---

*Stevens JC: Surgical Nutrition: The Fourth Coming, reprinted from Letters to the Editor. *JAMA* 239:192, 1978.

[1] Dudrick SJ, Wilmore DW, Vars HM, et al: Long-term parenteral nutrition with growth, development and positive nitrogen balance. *Surgery* 64:134-142, 1968.

We have reprinted the above letter to the editor of JAMA because we believe it should be seen by every physician concerned with the nutritional status of hospitalized patients. The letter writer ranks hyperalimentation with some of the monumental medical discoveries of the past—anesthesia, antisepsis and antibiotics. Few who have witnessed the lifesaving benefits of this technique would argue the point.

We at USV are proud of our continuing role in hyperalimentation through the development and refinement of the comprehensive multivitamin infusion M.V.I.®, as well as sponsorship of research and educational programs in parenteral nutrition.

To learn how hyperalimentation may reduce morbidity and mortality in a wide variety of clinical situations, just write us on your letterhead requesting a comprehensive monograph, tape-cassette program and/or film on the subject.

USV LABORATORIES

USV Laboratories, Division
USV Pharmaceutical Corp.
Tuckahoe, New York 10707

HYPERALIMENTATION

M.V.I.® (MULTI-VITAMI INFUSION)

THE CEPHALOSPORIN COST CONTAINMENT CALCULATOR.

"The determination as to which product to select has turned out to be almost entirely, if not entirely, on the basis of cost. Cephalothin and cephapirin...can be considered identical in terms of pharmacokinetics, therapeutic efficacy and toxicology. Also, in terms of therapeutic efficacy and toxicology, these two compounds are similar to cefazolin."*

—Richard Quintiliani, M.D.
Director, Division of Infectious Diseases
Hartford Hospital[1]

*Cephapirin, cephalothin and cefazolin are not chemically or generically equivalent and any statements made comparing these products are valid only when considering mutually approved indications.

Cephalosporins account for 39% of all hospital parenteral antibiotic purchases. That's a lot of cost to contain. But the potential for savings is great.

And, the only machine you'll ever need to calculate maximum cephalosporin savings is already on your desk.

For specific details on how Cefadyl can save money for your institution, just pick up your telephone and dial one of the toll-free numbers listed below.

Everyone talks about hospital cost containment. But Bristol Laboratories has a cephalosporin price worth talking about!

**Call the
Cefadyl Cost Containment Hotline
today–**

**In the Continental U.S.,
call toll-free**

800-448-5779

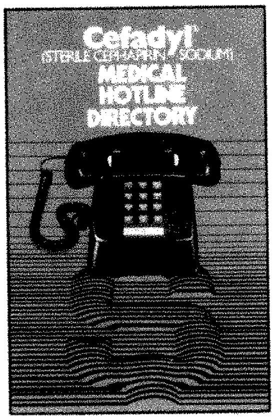
(In New York State, call toll-free 800-962-5746)

**Cefadyl®
(STERILE
CEPHAPIRIN SODIUM)
can save money!**

SEE NEXT PAGE FOR PRESCRIBING INFORMATION

Connect yourself to the Cefadyl® (STERILE CEPHAPIRIN SODIUM) MEDICAL HOTLINE–FREE!

The Cefadyl Medical Hotline Directory lists all the government agencies and private institutions that affect the practice of medicine in America today. And, for most listings, the Directory includes names and numbers of the key individuals, not just a general switchboard.



To obtain your free copy of the Cefadyl Medical Hotline Directory, just call toll-free
800-448-5779
in Continental U.S.
(New York State residents call toll-free
800-962-5746).

Cefadyl® (STERILE CEPHAPIRIN SODIUM) can save money!

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CEFADYL®
(sterile cephapirin sodium)
(7) Cefadyl 3/6/78

For complete prescribing information, please consult the Official Package Circular.

Contraindications

Cefadyl (sterile cephapirin sodium) is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

Warnings

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exceptions should be made with regard to Cefadyl.

If an allergic or anaphylactic reaction should occur, discontinue Cefadyl and institute appropriate treatment.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions

The renal status of the patients should be determined prior to and during Cefadyl therapy, since in patients with impaired renal function, a reduced dose may be appropriate.

Prolonged use of Cefadyl may result in the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken. With high urine concentrations of cephapirin, false-positive glucose reactions may occur if Clinitest, Benedict's Solution or Fehling's Solution are used. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Tes-Tape) be used.

Adverse Reactions

Hypersensitivity — Cephalosporins were reported to produce the following reactions: maculopapular rash, urticaria, reactions resembling serum sickness, and anaphylaxis. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—During large-scale clinical trials, rare instances of neutropenia, leukopenia, anemia were reported. Some individuals, particularly those with azotemia, have developed positive direct Coombs' test during therapy with other cephalosporins.

Liver—Elevations in SGPT or SGOT, alkaline phosphatase, and bilirubin have been reported.

Kidney—Rises in BUN have been observed; their frequency increases in patients over 50 years old.

How Supplied

Cefadyl (sterile cephapirin sodium) for I.M. or I.V. Injection. Cephapirin sodium equivalent to 1 Gm., 2 Gm., 4 Gm., or 20 Gm. cephapirin. For information on package sizes available, refer to the current price schedule.

1. Quintiliani R: The Cephalosporins: An Overview, film, (Feb) 1979.

BRISTOL®
©1979 BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, N.Y. 13201

Cancer

A Journal of the American Cancer Society, Inc.

TEN-YEAR CUMULATIVE INDEX OF SUBJECTS AND AUTHORS

VOLUMES 18–34. JANUARY 1965–DECEMBER 1974

The 10-year Cumulative Index to CANCER, printed in an easy-to-locate format is a convenient useful reference to the findings and developments in cancer as published in this official publication of The American Cancer Society during the years 1965 through 1974.

Completely cross-referenced, the key indexing words are those of the Medical Subjects Headings (MESH) of the National Library of Medicine.

In the Subject Index, under appropriate category headings set in bold face type, the complete title to each article is listed followed by author's name in parentheses, and the specific volume, page citation. Over 25,000 subject entries are included.

The Author Index, comprising some 10,000 entries, lists the principal author/s for each article and also cites volume and page location of the article.

In 328 pages, 7½ × 10¼, the outward appearance of the Cumulative Index matches that of the Journal CANCER itself. Price postpaid is $25.00 per copy. U.S., $26.00 all others.

CANCER

J. B. Lippincott Company

Attn. J. W. Bradley, Circulation Manager

East Washington Square, Philadelphia, Pa. 19105

Please send ______ copies of CANCER's Ten-Year Cumulative Index (1965–1974), at $25.00 per copy postpaid U.S. ($26.00 all others).

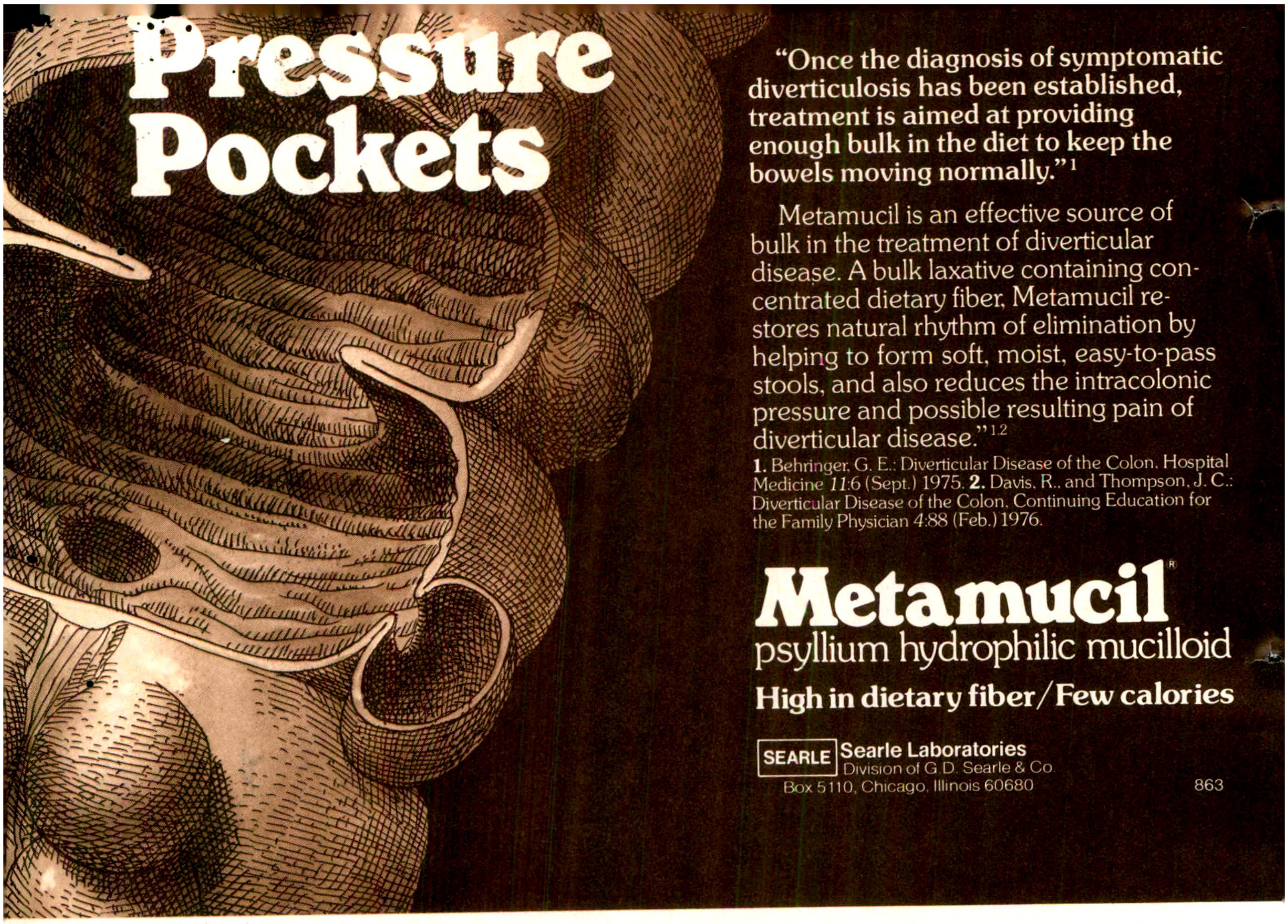
☐ Payment herewith ☐ Send Invoice

Name ______________________________

(Please Print)

Address ______________________________

City/State/Zip ______________________________



Pressure Pockets

"Once the diagnosis of symptomatic diverticulosis has been established, treatment is aimed at providing enough bulk in the diet to keep the bowels moving normally."[1]

Metamucil is an effective source of bulk in the treatment of diverticular disease. A bulk laxative containing concentrated dietary fiber, Metamucil restores natural rhythm of elimination by helping to form soft, moist, easy-to-pass stools, and also reduces the intracolonic pressure and possible resulting pain of diverticular disease."[1,2]

1. Behringer, G. E.: Diverticular Disease of the Colon, Hospital Medicine *11*:6 (Sept.) 1975. **2.** Davis, R., and Thompson, J. C.: Diverticular Disease of the Colon, Continuing Education for the Family Physician 4:88 (Feb.) 1976.

Metamucil®
psyllium hydrophilic mucilloid
High in dietary fiber/Few calories

SEARLE **Searle Laboratories**
Division of G.D. Searle & Co.
Box 5110, Chicago, Illinois 60680

863

Complications in Vascular Surgery

***Edited by* HUGH G. BEEBE, M.D.,**
With 18 Contributors.

Outstanding vascular surgeons from all sections of the country have pooled their composite experience and knowledge for this in-depth work. Each has written on a specific vascular complication and gives you the benefit of his expertise in this area. Three objectives are always in view: 1) To help you prevent complications where the causes are known and can be anticipated. 2) To provide you with a clear guide to the management of complications. 3) To establish a foundation of information from which you can deal logically and effectively with problems not described. This work reaps the benefit of significant appraisals of long-term follow-up studies that became possible during the last ten years.

402 Pages • 175 Illustrations • 1973 • $32.00

J. B. LIPPINCOTT CO.
East Washington Square, Phila., Pa. 19105

Please send me:

Complications in Vascular Surgery $32.00

☐ Payment Enclosed ☐ Charge and Bill me

Name ______________________

Address ______________________

______________________ Zip ________

AS 7/79

Lippincott

ENDO LABORATORIES TAMES THE POPPY—
TO BRING YOU

new **NUBAIN**®
nalbuphine HCl

ANALGESIA COMPARABLE TO MORPHINE,
WITH IMPORTANT DIFFERENCES

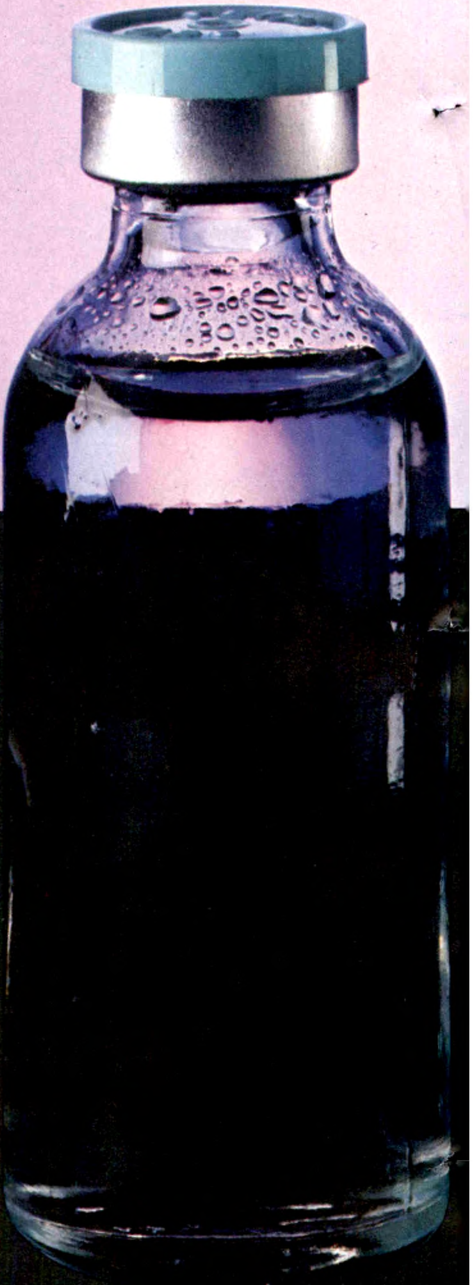
Please see complete prescribing information on last page of this advertisement

new

NUBAIN® AMPULS AND VIAL

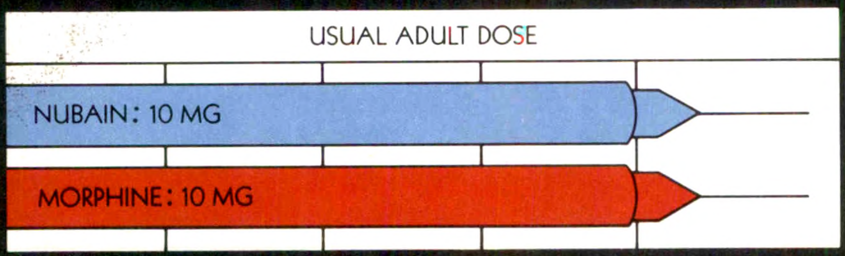
nalbuphine HCl

ANALGESIA COMPARABLE TO MORPHINE



NUBAIN offers:
onset, peak and duration
comparable to morphine

- 10 mg of NUBAIN is comparable in analgesic effect to 10 mg of morphine
- Onset of action with NUBAIN begins within 2 to 3 minutes I.V., and less than 15 minutes I.M. or S.C.
- Analgesic effect of NUBAIN lasts from 3 to 6 hours



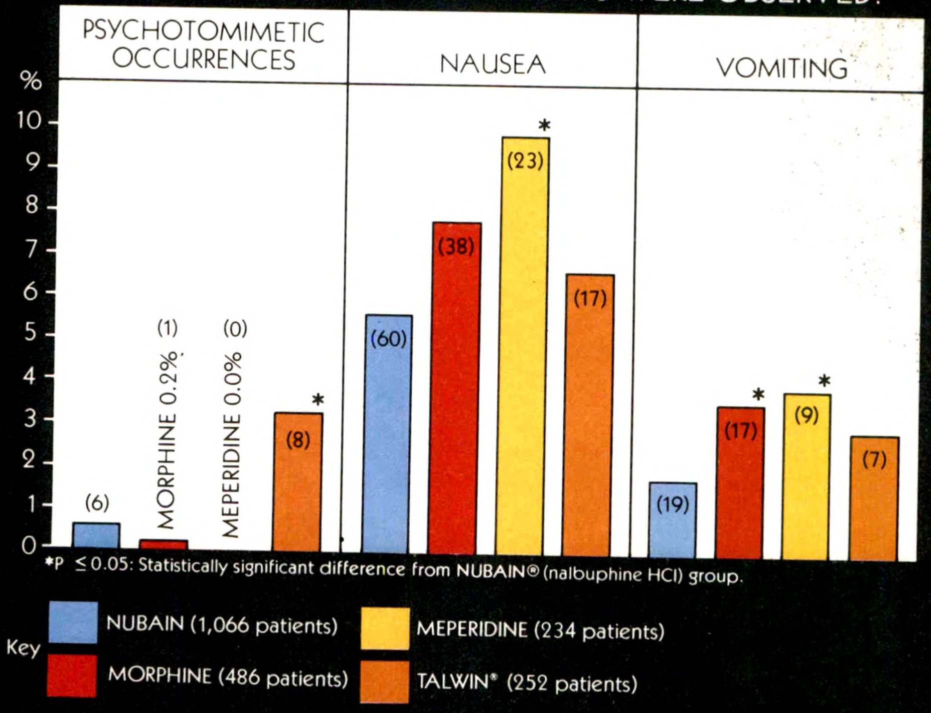
NUBAIN is an Endo registered U.S. trademark.

Please see complete prescribing information on last page of this advertisement.

WITH A LOW INCIDENCE OF SIDE EFFECTS

Clinical studies show: low incidence of nausea, vomiting and psychotomimetic effects

IN 27 SINGLE OR CROSS-OVER CLINICAL STUDIES (2,038 DRUG EVALUATIONS) THESE SIDE EFFECTS WERE OBSERVED:[1]



*P ≤0.05: Statistically significant difference from NUBAIN® (nalbuphine HCl) group.

[1] These clinical studies involved patients with pain from a variety of medical causes, including labor, cancer, and orthopedic and general surgical procedures. Actual number of patients experiencing each side effect is shown in parentheses on the bar graphs. Data on file, Endo Laboratories, Inc.

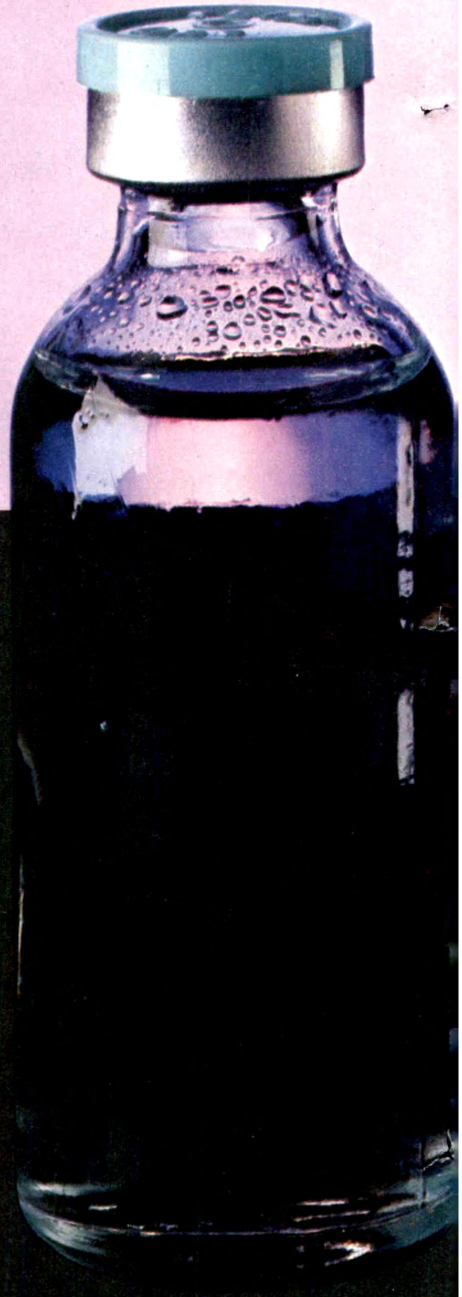
Endo DU PONT

new

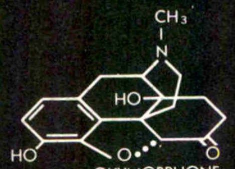
NUBAIN®

nalbuphine HCl

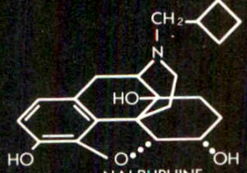
OFFERS LOW POTENTIAL FOR ABUSE



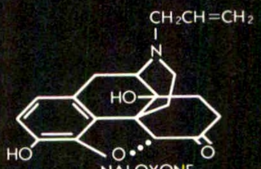
- NUBAIN requires no special storage or additional paperwork beyond your normal order or prescription.
- The unique properties of NUBAIN may be found in its molecular structure.



OXYMORPHONE



NALBUPHINE



NALOXONE

- Certain substances, such as NARCAN® (naloxone HCl), counteract or antagonize the effects and side effects of potent narcotics, such as morphine or NUMORPHAN® (oxymorphone HCl). NUBAIN was designed to incorporate important molecular features of the antagonist NARCAN and the potent analgesic NUMORPHAN, resulting in a drug with strong analgesia but limited abuse potential.

And a lower respiratory effect

- At dosages of 10 mg/70 kg, NUBAIN causes respiratory depression comparable to that of morphine. In contrast to morphine, higher doses of NUBAIN do not increase respiratory depression appreciably (see Precautions).

NARCAN is an Endo registered U.S. trademark.

NUMORPHAN is an Endo registered U.S. trademark.

Please see complete prescribing information on last page of this advertisement.

A clinical summary:

27 investigations evaluated more than 1,000 medical and surgical patients in regard to the effect of NUBAIN upon acute or chronic pain. Among these studies are the following, which highlight important areas of analgesic use:

- ORTHOPEDICS—this study encompassed 52 patients and compared NUBAIN to meperidine. Treatment varied from 1 to 40 days. NUBAIN was found to deliver satisfactory analgesia with no overt evidence of physical tolerance.
- CANCER—this study encompassed 37 patients treated for 1 to 186 days. Many of the patients stabilized on I.M. NUBAIN received dosages every 6-8 hours.
- OBSTETRICS—four double-blind studies were conducted encompassing 159 patients in labor. I.M. NUBAIN was compared to I.M. meperidine. Analgesically, both drugs were deemed similar (10-15 mg NUBAIN equal to 75-113 mg meperidine). Neonates did equally well on both drugs, but there is a possibility that either drug can produce depressive effects in the fetus or neonate. Mothers treated with NUBAIN had fewer side effects, and hospital personnel liked NUBAIN.
- Please see full prescribing information, including a complete discussion of adverse reactions, on following page.

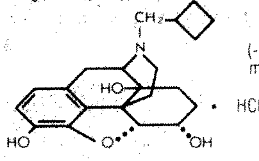
NUBAIN® (nalbuphine HCl)

Analgesia comparable to morphine, with important differences

new NUBAIN® nalbuphine HCl

DESCRIPTION

NUBAIN (nalbuphine hydrochloride) is a synthetic narcotic agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used narcotic antagonist, naloxone, and the potent narcotic analgesic, oxymorphone.



NALBUPHINE HYDROCHLORIDE

(-)-17-(cyclobutylmethyl)-4, 5α-epoxymorphinan-3, 6α, 14-triol,hydrochloride

Each ml of the injectable aqueous solution of NUBAIN contains 10 mg of nalbuphine hydrochloride.

ACTIONS

NUBAIN is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis.

Its onset of action occurs within 2 to 3 minutes after intravenous administration, and in less than 15 minutes following subcutaneous or intramuscular injection. The plasma half-life of nalbuphine is 5 hours and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours.

The narcotic antagonist activity of NUBAIN is one-fourth as potent as nalorphine and 10 times that of pentazocine.

INDICATIONS

For the relief of moderate to severe pain. NUBAIN can also be used for preoperative analgesia, as a supplement to surgical anesthesia, and for obstetrical analgesia during labor.

CONTRAINDICATIONS

NUBAIN should not be administered to patients who are hypersensitive to it.

WARNINGS

Drug Dependence NUBAIN has been shown to have a low abuse potential which is approximate to that of pentazocine. When compared with drugs which are not mixed agonist-antagonists, it has been reported that nalbuphine's potential for abuse would be less than that of codeine and propoxyphene. Psychological and physical dependence and tolerance may follow the abuse or misuse of nalbuphine. Therefore, caution should be observed in prescribing it for emotionally unstable patients, or for individuals with a history of narcotic abuse. Such patients should be closely supervised when long-term therapy is contemplated.

Care should be taken to avoid increases in dosage or frequency of administration which in susceptible individuals might result in physical dependence.

Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection.

Use in Ambulatory Patients NUBAIN may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, NUBAIN should be administered with caution to ambulatory patients who should be warned to avoid such hazards.

Use in Emergency Procedures Maintain patient under observation until recovered from NUBAIN effects that would affect driving or other potentially dangerous tasks.

Use in Children Clinical experience to support administration to patients under 18 years is not available at present.

Use in Pregnancy (other than labor) Safe use of NUBAIN in pregnancy has not been established. Although animal reproductive studies have not revealed teratogenic or embryotoxic effects, nalbuphine should only be administered to pregnant women when, in the judgement of the physician, the potential benefits outweigh the possible hazards.

Use During Labor and Delivery NUBAIN can produce respiratory depression in the neonate. It should be used with caution in women delivering premature infants.

Head Injury and Increased Intracranial Pressure The possible respiratory depressant effects and the potential of potent analgesics to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, NUBAIN should be used in these circumstances only when essential, and then should be administered with extreme caution.

Interaction With Other Central Nervous System Depressants Although NUBAIN possesses narcotic antagonist activity, there is evidence that in nondependent patients it will not antagonize a narcotic analgesic administered just before, concurrently, or just after an injection of NUBAIN. Therefore, patients receiving a narcotic analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUBAIN may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

PRECAUTIONS

Impaired Respiration At the usual adult dose of 10 mg/70 kg, NUBAIN causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of NUBAIN. Respiratory depression induced by NUBAIN can be reversed by NARCAN® (naloxone hydrochloride) when indicated. NUBAIN should be administered with caution at low doses to patients with impaired respiration (e.g., from other medication, uremia, bronchial asthma, severe infection, cyanosis or respiratory obstructions).

Impaired Renal or Hepatic Function Because NUBAIN is metabolized in the liver and excreted by the kidneys, patients with renal or liver dysfunction may overreact to customary doses. Therefore, in these individuals, NUBAIN should be used with caution and administered in reduced amounts.

Myocardial Infarction As with all potent analgesics, NUBAIN should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Tract Surgery As with all narcotic analgesics, NUBAIN should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

ADVERSE REACTIONS

The most frequent adverse reaction in 1066 patients treated with NUBAIN is sedation (381, 36%).

Less frequent reactions are: sweaty/clammy (99, 9%), nausea/vomiting (68, 6%), dizziness/vertigo (58, 5%), dry mouth (44, 4%), and headache (27, 3%).

Other adverse reactions which may occur (reported incidence of 1% or less) are:

CNS Effects nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine.

Cardiovascular Hypertension, hypotension, bradycardia, tachycardia.

Gastrointestinal Cramps, dyspepsia, bitter taste.

Respiration Depression, dyspnea, asthma.

Dermatological Itching, burning, urticaria.

Miscellaneous Speech difficulty, urinary urgency, blurred vision, flushing and warmth.

DOSAGE AND ADMINISTRATION

The usual recommended adult dose is 10 mg for a 70 kg individual, administered subcutaneously, intramuscularly or intravenously; this dose may be repeated every 3 to 6 hours as necessary. Dosage should be adjusted according to the severity of the pain, physical status of the patient, and other medications which the patient may be receiving. (See Interaction with Other Central Nervous System Depressants under WARNINGS.) In non-tolerant individuals, the recommended single maximum dose is 20 mg, with a maximum total daily dose of 160 mg.

Patients Dependent on Narcotics Patients who have been taking narcotics chronically may experience withdrawal symptoms upon the administration of NUBAIN. If unduly troublesome, narcotic withdrawal symptoms can be controlled by the slow intravenous administration of small increments of morphine, until relief occurs. If the previous analgesic was morphine, meperidine, codeine, or other narcotic with similar duration of activity, one-fourth of the anticipated dose of NUBAIN can be administered initially and the patient observed for signs of withdrawal, i.e., abdominal cramps, nausea and vomiting, lacrimation, rhinorrhea, anxiety, restlessness, elevation of temperature or piloerection. If untoward symptoms do not occur, progressively larger doses may be tried at appropriate intervals until the desired level of analgesia is obtained with NUBAIN.

Management of Overdosage The immediate intravenous administration of NARCAN® (naloxone hydrochloride) is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

The administration of single doses of 72 mg of NUBAIN intramuscularly to eight normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria.

HOW SUPPLIED

NUBAIN® (nalbuphine hydrochloride) injection for intramuscular, subcutaneous, or intravenous use (10 mg/ml) is available in:

NDC #0056-0385 10 mg/ml, 1 ml ampuls (box of 10)
NDC #0056-0384 10 mg/ml, 2 ml ampuls (box of 10)
NDC #0056-0386 10 mg/ml, 10 ml vials

Each ml contains 10 mg nalbuphine hydrochloride, 0.1% sodium chloride, 0.94% sodium citrate, 1.26% citric acid anhydrous, 0.1% sodium metabisulfite, and 0.2% of a 9:1 mixture of methylparaben and propylparaben as preservative; pH is adjusted with hydrochloric acid.

6094-1

Rev. March 1979

Endo Laboratories, Inc.
Subsidiary of the DuPont Company
Garden City, New York 11530

NUBAIN is an Endo Registered U.S. Trademark
NARCAN is an Endo Registered U.S. Trademark

Comparison of Estrogen Receptor Levels in Primary and Regional Metastatic Carcinoma of the Breast

J. L. HOEHN, M.D.,* E. D. PLOTKA, PH.D.,‡ K. B. DICKSON, M.D.†

The estrogen receptor (ER) level in carcinoma of the breast is a useful predictor of response to hormonal therapy. Metastatic disease may not have the same level of ER as the primary. In a series of 37 patients who had simultaneous ER determinations in both primary neoplasm and regional nodal metastasis there was 81% agreement. The true ER character of the tumor would have been missed in seven patients if only the primary tumor had been sampled. The possible reasons for this discrepancy are discussed. We feel that the nodal metastatic deposit may reflect the true nature of the ER status because it represents a purer concentration of tumor cells as well as representing the aggressive element of the tumor.

From the Departments of Surgery and Pathology,
Marshfield Clinic and the Marshfield Medical
Foundation, Inc., Marshfield, Wisconsin

THE DETERMINATION OF ESTROGEN receptors (ER) in carcinoma of the breast is a useful predictor of response to hormonal manipulation in patients with metastatic disease.[1,3,6] Unfortunately, when metastatic disease occurs, it may be in inaccessible or inconvenient locations, or the concentration of tumor cells may be insufficient to yield meaningful results. Therefore, it has been advocated that at the time of original biopsy the tumor be examined for ER.[2] One of the potential problems is that the metastatic disease may have a different ER level than the primary. Leclercq et al.[4] analyzed ER concentration in primary and metastatic disease in lymph nodes and concluded that with one exception the ER levels were the same. However, their data show considerable variation in the concentration of ER in the metastatic nodes and several cases with much higher ER concentrations in the invaded node than in the primary tumor.[4] Analysis of ER content in patients with sequential recurrent disease has revealed that ER level diminishes over time.[8,9] Block et al.[2] demonstrated that ER level in the primary tumor was a reliable method of choosing therapy for patients with metastatic disease. In the discussion of that paper[2] Shingleton stated an 80% correlation between the primary and metastatic disease in 410 patients. However, Webster et al.[10] and Rosen et al.[7] dissent with a difference of 28 and 24%, respectively in ER levels of primary and metastatic disease. In an attempt to understand the relationship between ER concentration in primary and metastatic disease, we have determined the ER level in both primary and regional metastatic carcinoma of the breast sampled simultaneously and compared the ER level in each and independently compared the histology in each.

Materials and Methods

Subjects

Estrogen receptors were determined on 129 patients with primary carcinoma of the breast seen at the Marshfield Clinic from March 1976 through December 1977, a 22 month period. Samples from both primary and regional metastatic disease in lymph nodes were obtained in 37 patients representing 28.6% of the entire group (Group A). All nodal disease was sampled from the axilla with the exception of one patient with a supraclavicular lymph node and all were done on the same day with the exception of one patient who underwent a lymph node biopsy of the axilla six days prior to her mastectomy. An additional 26 patients (Group B) underwent mastectomy and sampling of the primary tumor during the same 22 months but for a variety of reasons did not undergo ER sampling of the metastatic lymph node. The major reason was that in 17 of the 26 patients there was only a solitary node involved and in 77% of this group three or fewer nodes were involved, which were encountered only after routine histologic processing of the mastectomy specimen. The menstrual history breakdown is similar in both groups. The histologic make-up of both groups is also similar.

---

* Department of Surgery.

† Department of Pathology.

‡ Marshfield Medical Foundation.

Reprint requests J. L. Hoehn, M.D., Marshfield Medical Foundation, 510 North St. Joseph Avenue, Marshfield, Wisconsin 54449.

Submitted for publication: December 22, 1978.

0003-4932/79/0700/0069 $00.65 © J. B. Lippincott Company

The remaining 66 patients (52%) had no nodal metastases.

Technique

The samples were immediately taken to pathology where a portion was sectioned for histologic conformation and a portion was quick frozen in liquid nitrogen and stored at −70° until assayed. All ER assays were performed within one week of collection using a modification of the dextran-coated charcoal procedure described by Liskowski and Rose.[5] Briefly, the method is as follows: After thawing the samples, all uninvolved tissue was dissected away and the sample weighed and finely minced with a scissors. The minced tumor was transferred to a Potter-Elvehjem homogenizer with Tris-EDTA buffer, pH 8.0 (Trizma 8, Sigma Chemical Co., 10 mM; sucrose, 0.25 M; ethylene diamine tetraacetic acid sodium salt, 1 mM) and homogenized with six 10 second pulses of a con-Torque motor (Eberback Corp. Ann Arbor, MI) and resting intervals of 60 seconds. The homogenizer was kept immersed in an ice bath during the entire procedure. The homogenate was then centrifuged at 1,000 × g at 4° for 15 minutes and the supernatant (cytosol) transferred to another tube. At the same time, a homogenate of 30-day-old rat uterus was thawed and used as a positive control.

All samples were processed in sextuplet with three tubes used to assess total (T) binding and three tubes used to assess nonspecific (NS) binding. Two hundred femtomoles (fm) of ^{3}H-estradiol-17β (S.A. 110 Ci/mM) was added to each tube. Ten nanograms (ng) of cold estradiol-17β was also added to the NS tubes. A blank and ^{3}H-estradiol trace set was made by adding buffer (0.4 ml for blank × 3 and 0.9 ml for trace × 3) and 200 fm of ^{3}H-estradiol to six tubes. All tubes were mixed for 10 seconds on a vortex mixer and incubated for two hours at 20°. After incubation 0.5 ml of a dextran-coated charcoal suspension was added to all tubes except the ^{3}H-estradiol trace tubes. All tubes were mixed for 10 seconds and incubated for 10 minutes at 20° after which they were centrifuged at 40° and 500 × g for 15 minutes. The supernatant was decanted into counting vials and 10 ml of scintillation cocktail added.

TABLE 1. *Estrogen Receptor Status of Patients Having Primary and Regional Nodes Sampled Simultaneously*

Number	Per Cent	Primary	Node
17	46	Negative 0.56 ± 0.12*	Negative 0.70 ± 0.16
3	8	Positive 4.4 ± 0.4	Positive 4.5 ± 1.0
9	24	Positive 32.2 ± 6.4	Strongly positive 67.3 ± 9.8
7	19	Negative 1.9 ± 0.4	Positive 32.1 ± 9.5
1	3	Strongly positive 41.5	Positive 9.6

* mean ± SEM fm/mg protein.

TABLE 2. *Menstrual History, Histologic Status, and Estrogen Receptor Status of All Patients*

	Group A	Group B
Number of patients	37	26
Premenopausal	11 (30%)	9 (35%)
Histology: ductal and intraductal	28 (76%)	20 (77%)
T size		
T_1	5 (17%)	10 (38%)
T_2	17 (46%)	13 (50%)
T_3	11 (30%)	1 (4%)
ER positive	13 (35%) 26.5 ± 5.6	15 (58%) 43 ± 11.4*
ER negative	24 (65%) 0.94 ± 0.2	11 (42%) 0.4 ± 0.2

* mean ± SEM fm/mg protein.

An aliquot of each sample homogenate and rat uterine homogenate was assayed for protein concentration by the Lowry method.

Specific ER sites are expressed as femtomoles of receptor per gram of tissue or per milligram of protein after subtracting the NS binding.

Independently, the primary and metastatic node slides were reviewed by one of the authors (K.B.D.) comparing the histologic features. These findings were later correlated with differences in the ER level. The histologic criteria utilized were type of tumor, grade of tumor, per cent of cellularity, and per cent of necrosis. Comparisons between per cent of cellularity in ER positive and ER negative nodal tumors were analyzed by the Student's t-test.

Results

There was basic agreement of ER content in 81% of the 37 patients in which duplicate assays were obtained. Seventeen patients had ER negative primary and nodal disease. Thirteen patients had ER positive nodes and primary cancer. However, in nine of these the ER level in the nodal disease was considerably higher than the primary site. In one patient the ER concentration of the primary disease was higher than in the node which had only microscopic metastasis on review (Table 1). However, seven patients had primaries which were ER borderline or negative and had definitely positive nodal disease.

The incidence of ER positivity is considerably lower in Group A (35%) (Table 2)., Pathologic review of Group A patients revealed a greater degree of cellularity

TABLE 3. *Comparison of ER Status and Cellularity in Group A Patients*

Patients	ER Status		Per Cent Cellularity	
	Primary	Node	Primary	Node
17	–	–	58	73
7	–	+	64	85
9	+	++	58	89
3	+	+	53	68
1	++	+	40	Microscopic

in the lymph nodes in all groups, but higher cellularity in the nodes which were ER positive (Table 3). Other histologic features including per cent of necrosis, type, and grade of tumor did not correlate with ER level in this small series.

Discussion

One disturbing difference between Group A and Group B is the difference in the per cent of ER positivity. The cutoff level of ER from negative to positive was 3.0 fm/mg of protein.[5] Two of the seven patients in Group A were just below this level (2.78 and 2.98). If these two were considered positive, the ER rate of this group would be 40.5% as compared in Group B. Alternatively, if one assumes that all seven patients with ER negative primary which had ER positive regional nodal metastasis were in fact ER positive, the overall incidence of ER positivity in this group would be 54% which compares favorably with 58% in Group B. Tumor size did not seem to be a factor. Although in Group A 76% of the tumors were T_2 or T_3 in size as contrasted to 54% in Group B, in the seven patients in question, the large tumor size did not occur with any perdominance.

We feel that the concentration of cells bearing ER in the primary were not sufficient to reveal the same positive results as reflected in the lymph node. This is supported by the increased cellularity as seen on histologic study in the lymph node and further reflected in the nine patients in Group A where the nodal metastasis were distinctly more ER positive than the primary tumor. The per cent cellularity between groups in Table 3 was not significant because of the great variation in per cent cellularity within each group. Because of this variation in per cent cellularity, direct correlation with ER level is precluded. However, if cellularity is high, a larger fraction of the cells may contain ER. Whereas with low cellularity, even if ER is present, it may be diluted by non-ER bearing stroma or necrotic tumor. It is urged that metastatic nodal deposit be sampled for ER at the time of mastectomy in addition to the primary, in that because of a purer concentration of tumor cells, the true ER status of the tumor may be determined.

Acknowledgments

The authors wish to thank Ardis Eggert for her technical assistance and Loretta Keding and Alice Stargardt for their secretarial skills. This work was supported in part by monies donated by the V.F.W. Ladies Auxiliary.

References

1. Block, G. E., Jensen, E. V. and Polley Jr., T. Z.: The Prediction of Hormonal Dependency of Mammary Cancer. Ann. Surg., 182:342, 1975.
2. Block, G. E., Ellis, R. S., DeSombre, E. and Jensen, E. V.: Correlation of Estrophilin Content of Primary Mammary Cancer to Eventual Endocrine Treatment. Ann. Surg., 188: 372, 1978.
3. DeSombre, E. R., Smith, S., Block, G. E., et al.: Prediction of Breast Cancer Response to Endocrine Therapy. Cancer Chemother. Rep., 58:513, 1974.
4. Leclercq, G., Heuson, J. C., Deboel, M. C. and Mattheiem, W. H.: Oestrogen Receptors in Breast Cancer: A Changing Concept. Br. Med. J., 1:185, 1975.
5. Liskowski, L. and Rose, D. P.: Experience with a Simple Method for Estrogen Receptor Assay in Breast Cancer. Clin. Chim. Acta, 67:175, 1976.
6. McGuire, W. L.: Current Status of Estrogen Receptors in Human Breast Cancer. Cancer, 36:638, 1975.
7. Rosen, P. P., Menendez-Botet, C. J., Urban, J. A., et al.: Estrogen Receptor Protein (ERP) in Multiple Tumor Specimens from Individual Patients with Breast Cancer. Cancer 39:2194, 1977.
8. Singhakowinta, A., Potter, H. G., Buroker, T. R., et al.: Estrogen Receptor and Natural Course of Breast Cancer. Ann. Surg., 183:84, 1976.
9. Walt, A. J., Singhakowinta, A., Brooks, S. C. and Cortez, A.: The Surgical Implications of Estrophile Protein Estimations in Carcinoma of the Breast. Surgery, 80:506, 1976.
10. Webster, D. J. T., Bronn, D. G. and Minton, J. P.: Estrogen Receptor Levels in Multiple Biopsies from Patients with Breast Cancer. Am. J. Surg., 136:337, 1978.

Nondialysis Uses for Vascular Access Procedures

ALEXANDER M. GUBA, JR., M.D., MAJ, MC, GEORGE J. COLLINS, JR., M.D., F.A.C.S., LTC, MC,
NORMAN M. RICH, M.D., F.A.C.S., COL, MC, LOUIS KOZLOFF, M.D., MAJ, MC, PAUL T. McDONALD, M.D., LTC, MC

Chemotherapeutic agents, blood products and hyperalimentation solutions have been administered and recurrent diabetic ketoacidosis has been treated via vascular access procedures in 13 patients during the period from 1972 through 1977. Bovine heterograft, saphenous vein graft and the direct arteriovenous fistulae have been successfully utilized in the construction of arteriovenous fistulae in patients requiring vascular access for nonhemodialysis purposes. Operative techniques and therapeutic usefulness are discussed.

BRESCIA AND CIMINO[2] revolutionized the treatment of renal failure with their introduction of the arteriovenous fistula (AVF) for vascular access in 1966. This greatly simplified the problems associated with hemodialysis, and since then thousands of patients have benefited from repeated hemodialysis. Many techniques now exist for providing vascular access. The most commonly used ones are the external arteriovenous shunt and the saphenous vein arteriovenous fistulae in the forearm or lower extremity. In addition to saphenous vein, mandrils,[1] bovine heterografts,[6] umbilical veins,[4] and prosthetic conduits such as polytetrafluoroethylene[7,11,12] and Dacron®[10] have been used to create arteriovenous fistulae.

While the most common need for vascular access procedures is in patients with chronic renal failure, advances in oncology, medical treatment of diabetes mellitus, intravenous hyperalimentation for short gut syndrome, and treatment of hematologic disorders have created a subpopulation of patients requiring a readily available route for administration of medications or blood products. In some instances, the drugs administered cause sclerosis of veins. In others, previous thromboses or body habitus make use of the patient's own veins impossible. In such cases, creation of an arteriovenous fistula greatly facilitates therapy.[9]

From the Peripheral Vascular Surgery Service, Walter Reed Army Medical Center, Washington, D.C., The Division of Surgery, Walter Reed Army Institute of Research, Washington, D.C., and the Uniformed Services University of the Health Sciences, Bethesda, Maryland

This report summarizes the experience of the Peripheral Vascular Surgery Service, Walter Reed Army Medical Center during the past four years with patients who have had indications other than hemodialysis for vascular access procedures.

Materials and Methods

The records of all patients undergoing vascular access procedures for indications other than dialysis were reviewed. Our first experience with these procedures for indications other than hemodialysis was in November 1973, and all cases from then until November 1977 are included in the review.

The parameters considered pertinent to the review were age and sex of patients operated upon, primary diagnosis, indications for the procedure, type of procedure performed, morbidity, patency rates, and impact of the procedure on management of the specific disease state for which it was performed.

Results

In all, 13 patients ranging in age from 15 to 66 had vascular access procedures performed during the four year period from 1973 to 1977. The average age was 40. Three were men and ten were women. The diseases for which the procedures were performed are outlined in Table 1.

Overall, 14 bovine heterografts were used for construction of AVF's in 12 patients, while three saphenous vein grafts were used in two patients. As shown in Table 1, some patients had more than one fistula created. Seven distal forearm, radial artery to cephalic vein fistulae were created in four patients.

Nine of the ten patients needing vascular access for chemotherapy had bovine heterograft AVF's placed in

---

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Reprint requests: Alexander M. Guba, Jr., M.D., MAJ MC, Peripheral Vascular Surgery Service, Walter Reed Army Medical Center, Washington, D.C. 20021.

Submitted for publication: February 6, 1979.

0003-4932/79/0700/0072 $00.65 © J. B. Lippincott Company

TABLE 1. *Primary Diagnoses and Indications for Access Procedures*

Patient	Primary Disease	Indication
1	Hodgkin's disease	Chemotherapy
2	Gastric carcinoma	Chemotherapy
3	Esthesioblastoma (orbit)	Chemotherapy
4	Acute myelocythemic leukemia	Chemotherapy
5	Carcinoma of breast	Chemotherapy
6	Hodgkin's disease	Chemotherapy
7	Carcinoma of lung (Oat cell)	Chemotherapy
8	Acute myelocythemic leukemia	Chemotherapy
9	Multiple myeloma	Chemotherapy
10	Malignant teratoma	Chemotherapy
11	Short gut syndrome	Hyperalimentation
12	Diabetes mellitus	Insulin administration
13	Osler-Weber-Rendu syndrome	Transfusions

the arm. Anastomoses were done end-to-side from the brachial artery to either the cephalic vein, basilic vein, or brachial or axillary vein. The remaining patient had a radiocephalic fistula performed at the wrist level. The patient with short gut syndrome had a bovine heterograft fistula placed in the arm initially.

Patient 12, a 20-year-old diabetic had an initial attempt at creation of a fistula using bovine heterograft. This thrombosed in the early postoperative period. Because of her need for long-term access, an AVF using saphenous vein as the conduit was placed in the arm.

Multiple revisions of the initially created AVF's were necessary in some patients. In others, it became necessary to create an additional fistula in a different location. In all, 30 procedures were performed. The initial technique, number of revisions needed to maintain patency, and the total period of therapeutic usefulness in each patient is shown in Table 2. Despite the need to revise the fistulae in some patients and to create new fistulae in others, the access route has been useful in most patients. By providing continuous venous access, patient 11, with short gut syndrome, has been able to receive hyperalimentation at home for seven years. Patient 12, a difficult to manage juvenile diabetic, has been successfully resuscitated from frequent episodes of ketoacidosis via the AVF. Blood withdrawal for frequent laboratory tests has been greatly simplified in her case by the presence of the AVF. Several patients have been able to complete courses of chemotherapy, and others are continuing to receive chemotherapy.

Some of the procedures were done under general anesthesia, but most were done under regional or local anesthesia with sedation. The morbidity associated with the procedures was minimal. Two patients developed erythema and tenderness over bovine heterografts without evidence of infection. Both were treated with short courses of prednisone and responded rapidly. There were no deaths related to the procedures.

Discussion

Patients requiring vascular access for reasons other than dialysis frequently have difficult medical problems. Many have diseases with poor long-term prognoses. Superficial veins are most often not available for creation of access routes because of thrombosis secondary to repeated venipuncture and/or injection of sclerosing agents. In addition to the limited availability of veins for creating fistulae, venous outflow may also be limited. This jeopardizes the chances for long-term patency of fistulae that are successfully created. Another factor possibly contributing to decreased patency rates of fistulae in such patients is the administration of sclerosing agents such as hyperosmolar hyperalimentation solutions and chemothera-

TABLE 2. *Types of Access Procedures and Follow-up*

Patient	Initial Location	Initial Material Used	Number of Revisions*	Total Therapeutic Usefulness
1	Right arm	Bovine heterograft	0	7 months
2	Left arm	Bovine heterograft	0	1 month
3	Left arm	Bovine heterograft	0	7 months
4	Left forearm	Bovine heterograft	2	4 months
5	Left forearm	Bovine heterograft	0	3 months
6	Left arm	Bovine heterograft	1	3 weeks
7	Left forearm	Bovine heterograft	0	5 months
8	Right forearm	D.A.V.F.‡	0	Undetermined
9	Left arm	D.A.V.F.	1	7 months
10	Left arm	D.A.V.F.	0	4 months
11	Right arm	D.A.V.F.	9	7 years
12	Right arm	Bovine heterograft	3	20 months
13	Left forearm	D.A.V.F.	1	1 day†

* In five patients it was necessary to create a new access route.

† Patient expired of massive gastrointestinal hemorrhage despite multiple transfusions.

‡ Direct arteriovenous fistula (radiocephalic or brachio-basilic).

peutic agents through the fistulae. In addition the fact that there is a thrombotic predisposition in patients with malignancies is well known and may account, in part, for the rather high incidence of thrombosis in our patients.[5,8,13]

In our experience, both bovine heterografts and autogenous saphenous veins can be effectively used as arteriovenous conduits. Saphenous vein may be superior for long-term use. However, the bovine heterograft is certainly of use in selected patients. With bovine heterografts, the procedures can be performed under local anesthesia through limited incisions.

The role of the direct, side to side, arteriovenous anastomosis (radiocephalic or brachio-basilic fistula) in these types of patients is not clear. In patients with good long-term prognoses, a chronic fistula may be advantageous. In oncology patients requiring immediate access, the direct fistula requiring a maturation period may not be ideal. Our results with radiocephalic forearm fistulae for nondialysis indications have been dismal because of early thrombosis and we no longer use them. In this regard, it is important to point out that there is no "ideal" access procedure and one should be familiar with several such procedures. The medial brachial vein seems to be a rather constant anatomic structure of adequate size. Because of this and the excellent qualities of the brachial artery as a donor vessel, we have tended to favor use of the brachial artery—brachial vein fistula over the last several years.

In our experience, the most common cause of failure of bovine AVF's is pseudointimal and/or neointimal proliferation at the bovine-vein anastomosis.

When fistulae do fail, thrombectomy or thrombectomy with patch angioplasty may result in a functional fistula. However, repeated efforts to maintain patency of a fistula with inadequate arterial inflow or venous outflow will not be successful. Platelet inhibitory drugs such as aspirin, persantin, and sulfinpyrazone may prove to be useful adjuvants for improving long-term patency, but further studies are needed to define their exact role. The central high flow fistulae described by Buckley and coworkers may also be useful when the primary fistula has failed.[3]

With advances in medical oncology and the expanded use of intravenous hyperalimentation, the number of patients who could benefit from arteriovenous fistulae is sure to increase in the future. In fact, higher patency rates should be obtained if fistulae were constructed earlier in the course of disease at a time when venous outflow is sufficient to ensure adequate run-off.

References

1. Beemer, R. K. and Hayes, J. F.: Hemodialysis Using a Mandril Grown Shunt. Trans. Am. Soc. Artif. Int. Organs, 19:43, 1973.
2. Brescia, N. J., Cimino, J. E., Appel, K. and Hurwich, B. J.: Chronic Hemodialysis Using Venipuncture and Surgically Created Arteriovenous Fistula. N. Engl. J. Med., 275:1089, 1966.
3. Buckley, C. J., Manning, L. G. and Page, C. P.: Experience with Central High Flow Arteriovenous Fistulas in Patients Requiring Chronic Parenteral Chemotherapy on Hemodialysis. Am. J. Surg., 136:730, 1978.
4. Dardik, H., Ibrahim, I. M. and Dardik, I.: Arteriovenous Fistulas Constructed with Modified Human Umbilical Cord Vein Graft. Arch. Surg., 111:60, 1976.
5. Edwards, E. A.: Migrating Thrombophlebitis Associated with Carcinoma. N. Engl. J. Med., 240:1031, 1949.
6. Johnson, J. M. and Kenoger, M. R.: Bovine Graft Arteriovenous Fistula for Hemodialysis. Am. J. Surg., 128:728, 1974.
7. Johnson, J. M., Baker, L. D. and Williams, T.: Expanded polytetrafluoroethylene—A Subcutaneous Conduit for Hemodialysis. Dialysis Transplant., 5:52, 1976.
8. Kenney, W. E.: The Association of Carcinoma in the Body and Tail of the Pancreas with Multiple Venous Thrombi. Surgery, 14:600, 1943.
9. Lempert, N., Knight, E. and Karmody, A.: Vascular Access for Cancer Chemotherapy. JAMA, 237:1964, 1977.
10. Levowitz, B. S., Flores, L., Dunn, I. and Frumkin, E.: Prosthetic Arteriovenous Fistula for Vascular Access in Hemodialysis. Am. J. Surg., 132:368, 1976.
11. Mohaideen, A. H., Avram, M. M. and Mainzer, R. A.: Polytetrafluoroethylene Grafts for Arteriovenous Fistulae—Preliminary Report. N. Y. State J. Med., 76:2152, 1976.
12. Pasternak, B. M., Paruk, S., Kogan, S. and Levitt, S.: A Synthetic Vascular Conduit (Expanded PTFE) for Hemodialysis Access—A Preliminary Report. Vas. Surg., 11:99, 1977.
13. Thomson, A. P.: Thrombosis of the Peripheral Veins in Visceral Cancer. Clin. J., 67:137, 1936.

An in Vivo Evaluation of Microaggregate Blood Filtration During Total Hip Replacement

EDWARD L. SNYDER, M.D.,* PATRICIA S. UNDERWOOD, M.D.,† MORTON SPIVACK, M.D.,*
LAWRENCE DEANGELIS, M.D.,† EDWARD T. HABERMANN, M.D.‡

From the Departments of Internal Medicine, Anesthesiology, and Orthopaedics, Montefiore Hospital and Medical Center, Bronx, New York

In order to evaluate the effect of microaggregate blood filtration on pulmonary status, hemostatic status, and incidence of infection, a prospective study was performed on patients undergoing elective total hip replacement for osteoarthritis. Forty patients were randomized to either a 260 micron standard filter group or a 20 micron microaggregate filter group. Patients were monitored pre- and postoperatively for changes in arterial blood gases and *in vitro* test of hemostasis. Postoperative measurements were also made of the total volume of blood collected from the operative wound drain and of the number of infections incurred by patients in the two filter groups. Average transfusion was 4.0 units for the standard filter group and 4.6 units for the microaggregate filter group. Results showed that postoperatively, either immediately or after 48 hours, there were no statistically significant differences ($p > 0.05$) between either filter group for any of the tests of pulmonary or hemostatic function evaluated. For infection no trends were found to suggest that microaggregate filters conveyed any protective effect. These data suggest that routine microaggregate blood filtration of up to 5 units of blood is not required.

DATA FROM MILITARY[6] and civilian[9,10] trauma studies suggest that when transfused in large quantities, microaggregates play a role in the development of the adult respiratory distress syndrome. Furthermore, Solis and Gibbs[12] have postulated that infusion of microaggregates might produce a blockade of the reticuloendothelial system and thus contribute to the bleeding and infection seen after massive blood transfusion.

Few studies have evaluated these parameters in patients receiving low volume elective transfusions. To assess the *in vivo* effect of microaggregate blood filtration (MABF) on pulmonary function, hemostatic function, and incidence of infection, we designed a prospective randomized study on patients undergoing elective total hip replacement.

Materials and Methods

Patient Selection Criteria

From June 1977 through July 1978, using a table of random numbers, 40 patients undergoing elective total hip replacement for primary or secondary osteoarthritis were assigned to one of two filter groups (Table 1). Patients paired with an even number (SF group; n = 20) received all blood transfusions through a large pore 260μ standard filter (Saftifilter 834-30, Cutter Laboratories, Berkeley, CA). The other patients, matched with an odd number, (MF group; n = 20) received blood infused through a 20μ microaggregate blood filter (PFF-100, Bentley Laboratories, Irvine, CA).

To maintain uniformity between the two patient groups the following criteria were imposed:

1) Age: All patients were over 40 years of age.
2) Surgical history: All patients were scheduled for elective total hip replacement for either primary degenerative osteoarthritis or osteoarthritis secondary to previous hip surgery or trauma.
3) Medical history: Patients were free of clinically detectable renal, cardiovascular, pulmonary, hematologic, or systemic disease. Patients were excluded from the protocol if any of the following abnormalities were present:
   Renal: History of acute or chronic renal disease, serum creatinine over 1.3 mg/dl.
   Cardiovascular: History of right or left sided congestive heart failure, angina pectoris, recent cere-

---

* Department of Internal Medicine.

† Department of Anesthesiology.

‡ Department of Orthopaedics.

Presented in part at the Annual Meeting of the American Association of Blood Banks, November 4–9, 1978, New Orleans, Louisiana.

Supported in part by National Research Service Award 5 T32 HL07080 USPHS, (Dr. Snyder) and a grant from Bentley Laboratories, Inc.

Reprint requests: Edward L. Snyder, M.D., Yale-New Haven Hospital, 789 Howard Avenue, New Haven, Connecticut 06504.

0003-4932/79/0700/0075 $00.75 © J. B. Lippincott Company

TABLE 1. *Clinical Material*

	MF-20μ Filter	SF-260μ Filter
Patients	20	20
Mean age (range)	69 (40-86)	63 (40-81)
Sex (M/F)	3/17	3/17
Mean transfusion (range)	4.6 (2-9)	4.0 (2-7)

brovascular accident, clinical evidence of extensive peripheral vascular disease, EKG evidence of myocardial ischemia or acute cardiac arrhythmia, radiographic evidence of cardiomegaly, systolic hypertension over 180 mmHg and diastolic hypertension over 106 mmHg.

Pulmonary: History of obstructive or restrictive lung disease, chronic bronchitis, use of over one pack of cigarettes per day, abnormal chest radiograph, arterial blood gas on room air (FiO_2-.21) showing a Pa_{CO_2} over 42 mmHg and a PaO_2 less than 70 mmHg.

Hematologic: History of chronic bleeding diathesis, abnormal preoperative platelet count or prothrombin time.

Systemic: Presence of any systemic illness *i.e.*, sickle cell anemia, rheumatoid arthritis, or carcinoma.

Parameters Studied

Evaluation of MABF in these surgical patients included: 1) Hematologic (preoperative and two hours postoperative): hematocrit, hemoglobin, white blood count, plasma hemoglobin. 2) Clinical chemistry (preoperative and two hours postoperative): serum sodium, potassium, albumin, globulin. 3) Hemostasis (preoperative and two hours postoperative): platelet count, prothrombin time; volume of blood collected from the postoperative wound drain (1-72 hours postoperatively). 4) Pulmonary (preoperative, intraoperative, two hours postoperative, 48 hours postoperative): arterial pH, Po_2, Pco_2. 5) Infection: postoperatively until discharge patients were monitored for development of infection using the following criteria:

a) *Urinary tract infection:* Pyuria on urinanalysis with clean catch urine samples sent for culture reported as having over 100,000 bacterial colonies for females, or over 10,000 colonies for males.
b) *Septicemia:* Positive blood cultures.
c) *Operative wound infection:* clinical signs of infection and/or inflammation with positive bacterial cultures.
d) *Pulmonary infection:* clinical and/or radiographic evidence of consolidation or infiltration with positive sputum gram stain or culture.

Protocol

Informed consent was obtained from all patients in the study in accordance with the recommendations and approval of the Human Subjects Committee of Montefiore Hospital and Medical Center. Baseline preoperative clinical laboratory studies were drawn prior to surgery (Table 2). Preoperative arterial blood gases (PREOP) were obtained immediately prior to intubation while the patient was awake and breathing room air (FiO_2-.21). After induction and maintenance of anesthesia using a neurolept technique the patient was placed on a respirator with FiO_2 of .33. Thirty minutes after intubation, during the initial surgical skin incision, a blood gas (SI) was obtained through an indwelling radial artery catheter previously inserted for routine intraoperative patient monitoring. Additional blood gases were subsequently obtained after each unit of blood and 15 minutes after each of the two parts of the Charnley hip prosthesis were cemented into place using methylmethacrylate bone cement (MMA-1, MMA-2). During surgery, if the FiO_2 was altered for any reason, it was reset to .33 for 20 minutes prior

TABLE 2. *Clinical Laboratory Tests (n = 20) ± SEM*

	Preoperative*		2H Postoperative*	
Parameter	20μ-MF	260μ-SF	20μ-MF	260μ-SF
Hematocrit (%)	38.5 ± 0.9	37.8 ± 1.3	33.5 ± 1.0	35.6 ± 1.1
Hemoglobin (g/dl)	13.0 ± 0.4	12.8 ± 0.4	11.4 ± 0.4	12.0 ± 0.4
W.B.C. ($\times 10^9$/l)	7.3 ± 0.5	7.7 ± 0.6	12.2 ± 1.1	15.9 ± 1.6
Platelets ($\times 10^9$/l)	208.5 ± 12.4	228.6 ± 14.8	148.3 ± 13.6	163.6 ± 18.7
Plasma hemoglobin (mg/dl)	4.5 ± 0.5	5.0 ± 0.7	6.7 ± 0.7	6.4 ± 0.7
Sodium (mEq/l)	141 ± 0.6	141 ± 0.8	136 ± 1.1	136 ± 0.9
Potassium (mEq/l)	4.3 ± 0.1	4.2 ± 0.1	3.7 ± 0.1	3.7 ± 0.1
Albumin (g/dl)	4.3 ± 0.1	4.1 ± 0.1	3.5 ± 0.1	3.5 ± 0.1
Globulin (g/dl)	3.0 ± 0.1	3.2 ± 0.1	2.0 ± 0.1	2.3 ± 0.1
Prothrombin time (sec)†	10	10	11	11

* $p > 0.05$ (N.S.).

† Normal control = 10 seconds.

TABLE 3. *Preoperative and Postoperative Blood Gas Results* (FiO_2–.21)

MF-20μ Filter* ± S.E.M.				SF-260μ Filter* ± S.E.M.		
(n = 20) Preop	(n = 20) 2H-Post	(n = 13) 48H-Post		(n = 20) Preop	(n = 20) 2H-Post	(n = 14) 48H-Post
7.41 ± .01	7.39 ± .01	7.45 ± .01	pHa	7.40 ± .01	7.36 ± .01	7.44 ± .01
36.5 ± 1.2	37.5 ± 0.9	32.3 ± 0.8	Pa_{CO_2}	38.5 ± 0.8	40.2 ± 1.0	33.6 ± 0.9
80.4 ± 2.5	71.1 ± 3.0	73.5 ± 3.2	Pa_{O_2}	80.2 ± 2.3	71.5 ± 2.0	75.0 ± 2.4

* $p > 0.05$ (N.S.)

to resampling. A final intraoperative blood gas (SC) was obtained at the time of skin closure (FiO_2–.33) following completion of the procedure. Two hours postoperatively, the various blood tests listed in Table 2, and another blood gas (2H-POST) were obtained (FiO_2–.21). For most patients a blood gas was also obtained 48 hours postoperatively (48H-POST) via a single radial artery puncture with the patient breathing room air (FiO_2–.21).

All blood drainage collected via a Hemovac wound drain (Snyder Manufacturing Company, New Philadelphia, Ohio) was measured. The drain was routinely left indwelling up to 72 hours.

As part of routine care all patients received aminoglycoside antibiotics intraoperatively and for 24–48 hours postoperatively. All patients received intensive postoperative pulmonary toilette, and were encouraged to begin early ambulation.

Urine cultures were collected from all patients who developed a fever during the first two postoperative days. Subsequent cultures were obtained if the patient again became febrile, or developed clinical symptoms of urinary tract infection. Blood cultures were drawn on patients with either a high postoperative fever or with a new or persisting fever lasting over 24–48 hours. Cultures of the operative wound were taken from patients with clinical signs of infection such as delayed wound closure associated with erythema and serous drainage.

Pulmonary status was clinically monitored each day. Chest radiographs and sputum cultures were obtained from patients with postoperative fever and cough in whom a pneumonic process was suspected. This type of evaluation was initiated whenever a clinical diagnosis of pneumonia was considered in a patient, regardless of the amount of time that had elapsed since the day of surgery.

All transfused bloods were at least 12 days old. Collected data was analyzed using a parametric two-tailed Student's t-test for independent sets, and a nonparametric two-tailed Wilcoxson rank-sum test. The level of statistical significance used was $p < 0.05$.

Results

Evaluation of the clinical material is shown in Table 1. The comparison of clinical laboratory tests was made preoperatively to document additional similarity between the two filter groups, and postoperatively to exclude any harmful effects from the microaggregate filtration of blood in the amounts used in the study (Table 2). As seen there were no statistically significant differences between the two groups of surgical patients. Similarity in the preoperative and postoperative plasma hemoglobins for the two groups excluded clinically significant MABF-induced hemolysis.

Arterial blood gas results (Table 3) showed that on room air (FiO_2–.21) preoperatively and 2 hours postoperatively there were no differences ($p > 0.05$) between the two groups for either arterial pH, Pco_2 or Po_2. Blood gases sampled 48 hours postoperatively also failed to show any variation between the two sample populations. Similarly, arterial blood gases taken intraoperatively (Table 4) with patients intubated (FiO_2–.33) showed no difference between samples taken at the start of surgery (SI) and those obtained at the end of the operation during skin closure (SC) after all blood transfusions had been given. Blood gases

TABLE 4. *Intraoperative Blood Gas Results* (FiO_2–.33)

MF–20μ Filter (n = 20)* ± S.E.M.					SF–260μ Filter (n = 20)* ± S.E.M.			
SI	MMA-1	MMA-2	SC		SI	MMA-1	MMA-2	SC
7.43 ± .01	7.41 ± .01	7.41 ± .01	7.41 ± .01	pH_a	7.41 ± .01	7.41 ± .01	7.41 ± .01	7.40 ± .01
33.7 ± 1.2	33.8 ± 1.3	34.9 ± 1.2	35.1 ± 1.2	Pa_{CO_2}	35.9 ± 0.9	33.7 ± 1.2	34.5 ± 1.3	35.3 ± 1.2
115.7 ± 4.2	115.7 ± 5.6	108 ± 6.0	114.6 ± 6.2	Pa_{O_2}	121.3 ± 6.0	112.6 ± 5.5	112.2 ± 6.2	119.1 ± 6.7

* $p > 0.05$ (N.S.).

TABLE 5. *Postoperative Bleeding*

MF-20μ Filter* (n = 20)	SF-260μ Filter* (n = 20)
644 ± 54 ml	621 ± 69 ml

* ($p > 0.05$) (N.S.).

obtained five minutes after the hip prothesis was cemented into place (MMA-1, MMA-2) were unchanged from the values obtained during skin incision (SI). The volume of fluid intake and output was monitored for 48 hours postoperatively and showed no statistically significant differences ($p > 0.05$) between the two groups. None of the patients in either filter group developed clinical signs of respiratory distress postoperatively.

Patient tendency to hemorrhage (Table 5) evaluated by measurement of the total drainage from the operative wound site during the 72 hours that the wound drain remained indwelling, showed that the total volumes collected from both filter groups were comparable.

Routine evaluation of all patients in both filter groups revealed no evidence of preoperative infection. All patients entered into the study were afebrile, had chest radiographs which were negative for acute infiltration, urinanalyses which were negative for active urinary tract infection, and white blood counts which were within the normal limits for the laboratory.

Postoperatively all patients became febrile but defervesced within 72 hours unless a bacterial infection was found (Table 6). These transient febrile episodes were attributed to an inflammatory response to surgery. Postoperative urine cultures were obtained from all 40 patients in both groups during the first 24–48 hours and subsequently as described in the protocol. At the end of the study only six infections had been documented in the 20μ filter group and four infections verified in the 260μ filter group. Exclusion of those patients who had indwelling bladder catheters reduced the incidence of urinary tract infection to only two patients in each filter group.

No patient developed a bacteriologically proven deep wound infection during the course of the study, and in only one patient was the diagnosis considered. Although a superficial wound infection was suspected in 11 of the 40 study patients, only seven of the 11 patients evaluated had positive bacterial cultures. *Staphylococcus epidermidis* was the predominant organism cultured from the skin of three patients in the MF group and three of four patients in the SF group (Table 6).

Blood cultures were obtained from 35% of the patients in the 20μ MF group and 30% of the patients in the 260μ SF group. All of the cultures were sterile. Postoperatively none of the patients in either group developed respiratory distress. During the course of the study chest radiographs were ordered for seven patients in the microaggregate filter group and six patients in the standard filter group. Although atelectasis was reported on several of the postoperative films, none of the radiographs disclosed any evidence of acute infiltration or consolidation. Sputum cultures on the patients studied were reported as "normal flora."

Discussion

For the parameters investigated in our study no evidence was found that any benefit accrued to patients who received microaggregate filtered blood in the amounts used. We evaluated two sets of blood gas determinations, one set pre- and postoperatively while the patients were spontaneously breathing room air (FiO_2-.21), and the second set intraoperatively during anesthesia (FiO_2-.33). This provided a method of double checking the results since blood gases collected during spontaneous respiration could have been influenced by hypoventilation either from preoperative sedation or from postoperative incisional pain. No discrepancies between the two sets of data were found.

No reduction in postoperative hemorrhage was found in those patients receiving microaggregate filtered blood. For infections the numbers were too small to permit statistically significant conclusions.[8] Rather we were interested in trends which might imply a protective effect attributable to use of microaggregate filters. No such trends were seen.

Although a blockade of the reticuloendothelial system may be involved in the increased bleeding and infection reported after massive transfusions, we could not document that either of these clinical findings occurred after the transfusion of up to five units of blood in our patients.

TABLE 6. *Postoperative Infection*

	MF-20μ Filter (n = 20)		SF-260μ Filter (n = 20)	
Parameter	Patients Evaluated	Patients Positive	Patients Evaluated	Patients Positive
Fever (+ 38°)	20	20	20	20
Septicemia (blood cultures)	7	0	6	0
Deep wound infection	1	0	0	0
Superficial wound infection	5	3*	6	4**
Pneumonia	7	0	6	0
Urinary tract infection				
total	20	6	20	4
without catheter	7	2†	8	2‡

**Staphylococcus epidermidis* -3. ***Staphylococcus epidermidis* -3; *Proteus sp.* -1. †*Proteus sp.* -2. ‡*Pseudomonas aeruginosa* -2.

The number of microaggregates infused with four–five units of blood ($3-3.5 \times 10^8$) may have been insufficient to affect the reticuloendothelial system.[11] Alternatively, additional factors not detectable in our patients such as sustained hypotension, disseminated intravascular coagulation or hypovolemic shock may be playing a major causative role in the development of the bleeding and infection seen in massively transfused trauma patients.

Our study documented a lack of changes in arterial blood gases in the SF group up to 48 hours posttransfusion by which time significant changes in pulmonary gas exchange should have become detectable. Sensitive tests of pulmonary function have been able to detect some alterations in gas exchange after low volume transfusions, however, these changes have not been found consistently. For patients transfused with less than 3000 ml of blood, Takaori et al.[13] reported some adverse changes in pulmonary dead space (V_D/V_T) but no alterations in pulmonary shunting (Qs/Qt). Barrett et al.[1] found abnormalities in Qs/Qt in patients receiving several units of blood through a standard 170μ filter, but none in patients receiving microaggregate filtered blood. Virgilio et al.[14] however, reported finding no alterations in pulmonary function tests for 20 patients receiving an average of six–seven units of blood through a 170μ filter. None of the patients described in these three studies developed any clinical signs of respiratory distress.

The relationship between transfusion and subsequent hypoxemia was recently examined in a retrospective analysis of Vietnam combat casualties. Collins' group[4] concluded that differences in Pa_{O_2} noted in soldiers studied were more likely related to the type and the magnitude of injury sustained than the amount of blood transfused.

Of the over 6 million units of blood estimated to be transfused yearly in the United States,[7] the majority of patients receive less than four units. Since patients receiving low volume transfusions through standard pore filters are clinically asymptomatic with no evidence of hypoxemia, there seems to be little scientific justification for the proposal made by some authors[5,13] that MABF should be used routinely regardless of the volume of blood infused. Even the data reported by Reul[9,10] showing a need for MABF in massively transfused patients has been questioned, due to differences between the two groups of patients compared.[2,3] Economic factors also enter into the decision to use MABF for all transfusions. At present, a MABF-administration set costs several dollars more than a standard blood administration set.

It is possible that while the healthy lung can compensate for microaggregate emboli, a diseased lung cannot. Controlled studies evaluating the effect of low volume transfusions in patients with compromised pulmonary function are lacking; routine use of MABF in such patients may be of value.

Based on our study of arterial blood gases, bleeding tendency, and infection rate, we conclude that routine microaggregate blood filtration of up to five units of blood is not required.

Acknowledgments

The authors wish to thank Mrs. R. Condon for excellent secretarial assistance.

References

1. Barrett, J., Tahir, A. H. and Litwin, M. S.: Increased Pulmonary Arteriovenous Shunting in Humans Following Blood Transfusion. Arch. Surg., 113:947, 1978.
2. Bredenberg, C. E.: Does a Relationship exist between Massive Blood Transfusions and the Adult Respiratory Distress Syndrome? Vox Sang., 32:311, 1977.
3. Collins, J. A.: Does a Relationship Exist between Massive Blood Transfusions and the Adult Respiratory Syndrome? Vox Sang., 32:313, 1977.
4. Collins, J. A., James, P. M., Bredenberg, C. E., et al.: The Relationship Between Transfusion and Hypoxemia in Combat Casualties. Ann. Surg., 188:513, 1978.
5. Donham, R. T.: Rationale and Indications for Microfiltration of Blood in Emergency Medicine. Med. Instrum., 11:344, 1977.
6. Moseley, R. V. and Doty, D. B.: Death Associated with Multiple Pulmonary Emboli Soon After Battle Injury. Ann. Surg., 171:336, 1970.
7. National Heart and Lung Institute's Blood Resource Studies—Summary Report. DHEW Publication No. (NIH)73-416. June 30, 1972. DHEW, Bethesda, Maryland p. 27.
8. Rangno, R. E.: The Rationale of Antibiotic Prophylaxis in Total Hip Replacement Arthroplasty. Clin. Orthop., 96:206, 1973.
9. Reul, G. J., Greenberg, S. D., Lefrak, E. A., et al.: Prevention of Post-traumatic Pulmonary Insufficiency. Arch. Surg., 106: 386, 1973.
10. Reul, G. J., Beall, A. C. and Greenberg, S. D.: Protection of the Pulmonary Microvasculature by Fine Screen Blood Filtration. Chest, 66:4, 1974.
11. Shulman, N. R., Weinrach, R. S., Libre, E. P. and Andrews, H. L.: The Role of the Reticuloendothelial System in the Pathogenesis of Idiopathic Thrombocytopenic Purpura. Trans. Assoc. Am. Phys., 78:374, 1965.
12. Solis, R. T. and Gibbs, M. B.: Microaggregates in Stored Blood: Formation and Removal. *In* Chaplin, H., Jaffe, E. R., Lenfant, C. and Valeri, C. R. (eds.) Preservation of Red Blood Cells. Sponsored by Committee on Red Blood Cell Preservation, Division of Medical Sciences, National Research Council, June 5–6, 1972. National Academy of Sciences, Washington, D.C. p. 309.
13. Takaori, M., Nakajo, N. and Ishii, T.: Changes of Pulmonary Function Following Transfusion of Stored Blood. Transfusion, 17:615, 1977.
14. Virgilio, R. W., Smith, D. E., Rice, C. L., et al.: To Filter or not to Filter (Abstract). Inten. Care Med., 3:144, 1977.

Anoxic Hypothermic Cardioplegia Compared to Intermittent Anoxic Fibrillatory Cardiac Arrest

Clinical and Metabolic Experience with 1080 Patients

STEVEN J. PHILLIPS, M.D., ROBERT H. ZEFF, M.D., CHAM KONGTAHWORN, M.D., L. A. IANNONE, M.D., THOMAS M. BROWN, M.D., DAVID F. GORDON, M.D.

Appropriately applied, hypothermic cardioplegia allows an excellent surgical setting that can significantly reduce the myocardial ischemic injury resulting from anoxia. One thousand eighty adult and pediatric patients underwent a variety of corrective cardial surgical procedures utilizing cold potassium cardioplegic solution injected into the coronary arteries via the aortic root. Myocardial septal temperature was maintained at 18–20° during arrested time. This group of patients was compared to a group of 220 patients that underwent intermittent normothermic ischemic arrest to perform cardiac surgical procedures. Significant reduction in morbidity, mortality, perioperative myocardial infarction was noted in favor of the cardioplegic group. Metabolic coronary sinus blood analysis in the group undergoing surgery with cardioplegia revealed favorable changes in myocardial lactate and oxygen extraction.

From the Section of Cardiovascular Medicine and Surgery, Mercy Hospital, Des Moines, Iowa

THE IDEAL METHOD for myocardial protection during cardiac surgery has yet to be described. Few investigators would question the metabolic and morphological advantages of appropriately applied coronary perfusion for myocardial preservation in the beating nonworking heart.[6,19,22] The technical disadvantages[10] of continuous coronary artery perfusion during cardiac surgery has resulted in the use and advocation of nonperfusion methods.[24,26,27] Anoxic fibrillatory cardiac arrest provides a quiet operative field but has been criticized because its prolonged use can be associated with irreversible metabolic and ultrastructural damage.[5,8,12,16,18,21,25] Hypothermia combined with the infusion of "protective" solutions into the coronary circulation prior to and during anoxic arrest allows a quiet operative field and can provide significant myocardial preservation.[4,7,9,13–15,23,28,29] Cardiac arrest in diastole (cardioplegia) combined with hypothermia can be induced by a variety of techniques and is gaining widespread acceptance among cardiac surgeons.[1,3,11,17]

This report compares the clinical and metabolic results of a group of patients operated upon utilizing anoxic fibrillatory arrest vs. a group of patients operated upon utilizing anoxic hypothermic cardioplegia.

Materials and Methods

From July, 1974 through December 1977, 1080 adult and pediatric patients underwent a variety of corrective cardiac surgical procedures at Mercy Hospital, Des Moines, Iowa. Group I, 220 patients (July 1974–July 1975) were operated on utilizing intermittent anoxic fibrillatory arrest and Group II, 860 patients (July 1975–December 1977) had cardiac surgery utilizing continuous anoxic hypothermic cardioplegia.

Surgical Technique

Operative techniques were similar for both groups. A midsternal approach, disposable bubble oxygen, nonblood prime, systemic hypothermia (28–34°) and flow rates of 1.8–2.4 l/m^2 were used. Aortic and atrial cannulation usually without left ventricle venting was standard.[20]

Anoxic fibrillatory arrest (Group I). The technique for anoxic fibrillatory arrest was as follows: For coronary artery surgery a distal anastomosis was carried out during a 7–14 minute period of aortic crossclamping with electrically induced ventricular fibrillation. With completion of the distal anastomosis the aorta was unclamped and the proximal anastomosis carried out with the heart beating and perfused. All valvular surgery and congenital repair was carried out during

---

Reprint requests: Steven J. Phillips, M.D., Section of Cardiovascular Medicine and Surgery, Mercy Hospital, Des Moines, Iowa 50314.

Submitted for publication: December 18, 1978.

0003-4932/79/0700/0080 $00.70 © J. B. Lippincott Company

intermittent periods of anoxia no longer than 20 minutes alternating with three to five minutes of coronary perfusion with the heart beating. Average total crossclamp time for the 220 patients was 26 minutes with a range of 5–110 minutes.

Cardioplegia (Group II). The cardioplegic solution consists of 5% dextrose in water containing 20 meq/l potassium chloride buffered to a pH of 7.5 with sodium bicarbonate (2.4 meq/l). The osmolarity is 310 miliosmoles, Po_2-44 mmHg, solution temperature is 4°. The solution is rapidly injected into the aortic root at the onset of aortic crossclamping. The initial solution dose averaged 6 cc/kg. Cold saline (4°) is poured on the heart at this time. Myocardial septal temperature is monitored with a thermistor† and maintained between 18° and 22° by periodic topical hypothermia and bolus injection of the solution. Intermittent suction can be applied to the aortic injection catheter to decompress the aortic root of fluid and provide a dry operative field. All distal anastomosis, valve replacements or congenital repair are carried out during a single aortic crossclamp period. Average crossclamp time for the 860 patients was 38 minutes with a range of 6–120 minutes.

Clinical Studies

Assessment of recovery of cardiac electrical function was made by noting the frequency of defibrillatory shocks and time for normalization of the electrocardiogram following crossclamp release. Return of cardiac mechanical function was assessed by the necessity for catecholamine and/or intra-aortic balloon pumping the excessive pump support (low output syndrome). The perioperative infarction rate in the coronary revascularization group was determined by the electrocardiographic appearance of Q-waves and/or the presence of the myocardial fraction of creatine phosphokinase or lactic dehydrogenase. The perioperative myocardial infarction rate, mortality rate, cardiopulmonary bypass time, crossclamp time and total operative time was compared in both groups.

Metabolic Studies: Cardioplegia Only (Group II)

In 47 patients, a balloon-tipped catheter was wedged in the coronary sinus at the time of surgery. Coronary sinus blood was collected prior to aortic crossclamping (Group A) and three minutes after re-establishment of coronary perfusion (Group B). Each patient acted as its' own control and Group A was compared to Group B. Central aortic blood was collected in conjunction with lactate studies. Coronary sinus blood was analyzed for lactate, myocardial creatinine phosphokinase, pH, Pco_2, O_2, and potassium. Pre- and postcrossclamp myocardial lactate extraction ratios and cardiogenic lactate were calculated by:

$$\text{Myocardial Lactate Extraction Ratio} = \frac{\text{Aortic Lactate} - \text{Coronary Sinus Lactate}}{\text{Aortic Lactate}}$$

$$\text{Cardiogenic Lactate} = \text{Aortic Lactate} - \text{Coronary Sinus Lactate}$$

Pre- (Group A) vs. Post- (Group B) crossclamp data were compared and the statistical significance of the data determined by the Student's t-test.

Results

Surgical Technique

Both intermittent anoxic fibrillatory arrest (Group I) and hypothermic cardioplegia (Group II) provided a flaccid heart and a quiet operative field.

Cessation of myocardial electrical–mechanical activity was more complete with cardioplegia than intermittent anoxic arrest. Diastolic arrest occurred during the first 30–60 seconds of hypothermic cardioplegia solution administration as it typically took 180–240 seconds ($p < 0.001$) with electrical fibrillation. Myocardial septal temperature usually reached 18–20° with an initial bolus of 400 cc (6cc/kg) of this solution of topical hypothermia. Administration time for this initial bolus averaged 90 seconds. Reinjection of 100 cc of solution, each 15–20 minutes, was sufficient to maintain myocardial temperature at about 20°. The average volume of solution used per patient was 800 cc. The pressure in the aortic root at the injection site during injection averaged 60 mmHg.

Clinical Studies

In the fibrillatory anoxic arrest group (Group I) electrical defibrillation was required in more than 95% of the patients after crossclamp release. Spontaneous sinus rhythm following release of the crossclamp with normalization of the electrocardiogram was noted in 90% of the cardioplegic (Group II) patients within three minutes of coronary reperfusion ($p < 0.001$). Catecholamines alone (21 patients, 2.4%) or combined with intra-aortic balloon pumping (13 patients, 1.5%) was necessary in 44 (5%) of the 860 cardioplegic patients following surgery. The overall mortality rate in this group was 1.3% (11 patients). No correlation between the length of aortic crossclamping and mortality was noted. In Group II (fibrillatory anoxic arrest) use of

---

† Yellow Springs Instrument Co. Inc., Scientific Division, Yellow Springs, OH 45387.

TABLE 1. *Clinical Observations of Anoxic Hypothermic Cardioplegia Arrest Compared to Anoxic Fibrillatory Arrest*

	Group I Ischemic Arrest 220 Patients	Group II Hypothermic Cardioplegia 860 Patients	p Value
Defibrillation	Necessary 95 + %	Spontaneous 90%	0.001
Catecholamine Use	11% (25 pts.)	2.4% (21 pts.)	0.01
Balloon Pump	4% (8 pts.)	1.5% (13 pts.)	0.05
Mortality Rate	6% (12 pts.)	1.3% (11 pts.)	0.001
Perioperative MI	14% (31 pts.)	4% (34 pts.)	0.001
Crossclamp Time	26 min. (7–110 min)	38 min. (6–120 min)	0.01

catecholamines alone (25 patients, 11%) or combined with intra-aortic balloon pumping (8 patients, 4%) was necessary in 33 patients (15%) following surgery ($p < 0.001$). The mortality rate in this group was 6% (12 patients) as compared to Group I, 1.6% ($p < 0.001$). The perioperative myocardial infarction rate with cardioplegia in the coronary artery revascularization group was 4%. This was a significant reduction ($p < 0.001$) from a previous rate of 14% in the patients operated on with fibrillatory anoxic arrest (Table 1). Group II compared to Group I revealed a 20% reduction in pump time ($p < 0.01$) and a 15% reduction in total operative time ($p < 0.05$). No complications occurred because of the hypothermic cardioplegic technique.

Metabolic Studies (Cardioplegic Group Only)

Analysis of coronary sinus blood prior to anoxia (Group A) *vs.* three minutes after reperfusion of the coronaries (Group B) revealed significant changes ($p < 0.0005$) in pH (7.40 ± 0.06 vs. 7.34 ± 0.06), P_{CO_2} (37 ± 8 vs. 45 ± 7), and potassium (5.1 ± 0.9 vs. 6.5 ± 0.9). There were no significant changes (Group A *vs.* Group B) in P_{O_2} (44 ± 11 vs. 43 ± 10), cardiogenic lactate (0 ± 4 vs. 3 ± 4) or myocardial lactate extraction (0.8 ± 13 vs. −9.4 ± 21) (Table 2). Individual patient analysis of lactate metabolism revealed (Group A *vs.* Group B) that 17 patients extracted more lactate, 19 patients produced more lactate, and 11 remained unchanged following crossclamp release. No correlation was noted between the length of aortic crossclamp and the above data. Myocardial creatinine phosphokinase was present in two of the 47 patients. Both patients subsequently demonstrated perioperative myocardial infarction by EKG and enzyme criteria.

Discussion

Myocardial preservation is maximal when the non-working bypassed heart is allowed to beat while it is perfused with oxygenated blood.[5] The technical aspects of cardiac surgery often require a quiet, dry operative field making the above form of myocardial protection impractical. Anoxic cardiac arrest, which provides the optimal surgical environment, must be combined with some form of myocardial preservation in order to reduce the ischemic injury that results from anoxia.[5,8,12,16,18,21,25]

There is general consensus in the literature that myocardial ischemic injury can be minimized if the oxygen demands of the myocardium are reduced and its high energy substrates preserved during the period of anoxia.[1,4,14,27–29] This situation can be achieved by an appropriately applied technique of hypothermic cardioplegia.

Global myocardial hypothermia to 20° reduces myocardial oxygen demand by approximately 95%; rapid cardiac arrest created by a potassium-rich solution should help preserve high energy substrates; and flushing of the coronary artery with the cardioplegic solution should "wash out" platelet aggregates that might jeopardize the microcirculation. Our technique, described above, for global myocardial hypothermia is effective in maintaining the myocardial temperature at 20°. We want to emphasize the importance of monitoring myocardial temperature and the need for reinjection of the cold solution to maintain the cardiac temperature at 20°.

Most of the oxygen demand of the myocardium is utilized for electromechanical activity. The rapid conversion of the beating heart to flaccid arrest by potassium-containing hypothermic solution reduces myocardial oxygen demands and preserves myocardial high energy substrates.[1,9,13,23] The marked reduction of myocardial metabolism in our series was accomplished by the rapid induction of flaccid arrest and maintenance of hypothermia throughout the period of anoxic arrest.

The findings that no significant changes occurred in our myocardial lactate extraction ratio or cardiogenic lactate infer that anaerobic metabolism was minimal during the period of anoxia. The fact, the significant increase in P_{CO_2} during the anoxic period, as pointed out by Bleese, et al.,[2] indicates that oxidative metabolism may be maintained by the slightly hypertonic

TABLE 2. *Cardioplegic Arrest. Myocardial Metabolic Studies Prior to and Three Minutes Following Coronary Reperfusion in Group II (Cardioplegic Arrest)*

Parameter Studied	Pre Crossclamp Group A	Post Crossclamp Group B	T-Test P
pH	7.40 ± 0.06	7.34 ± 0.06	0.0005
P_{CO_2}	37 ± 8	45 ± 0.06	0.0005
P_{O_2}	44 ± 11	43 ± 10	0.0005
K	5.1 ± 0.9	6.5 ± 0.9	NS
Lactate Extraction Ratio	0.8 ± 13	−94 ± 21	NS
Cardiogenic Lactate	0 ± 4	+3 ± 4	NS

(310 miliosmols), glucose (5%) and oxygen (Po_2-44) containing cardioplegic perfusate. The significant rise in coronary sinus potassium following anoxia indicates the continued effect and presence of the cardioplegic solution.

Compared to our previous technique of fibrillatory anoxic arrest with intermittent coronary perfusion, hypothermic cardioplegia allowed a significant reduction in the morbidity, mortality, perioperative myocardial infarction rate, cardiopulmonary bypass time and operative time.

Summary

Appropriately applied, hypothermic cardioplegia allows an excellent surgical setting that can significantly reduce the myocardial ischemic injury resulting from anoxia. Improved hemodynamic, metabolic and clinical data indicate that this technique is favorable as compared to anoxic cardiac arrest with intermittent coronary perfusion.

The authors emphasize the importance of rapid cardiac arrest (cardioplegia) at the onset of anoxia and the maintenance of global hypothermia (20°) throughout the anoxic period.

References

1. Adappa, M. G., Jacobson, L. B., Helzer, R., et al.: Cold Hyperkalemic Cardiac Arrest Versus Intermittent Aortic Cross-Clamping and Topical Hypothermia for Coronary Bypass Surgery. J. Thorac. Cardiovasc. Surg., 75:171, 1978.
2. Bleese, N., Doring, V., Kalmar, P., et al.: Intra-operataive Myocardial Protection by Cardioplegia In Hypothermia: Clinical Findings. J. Thorac. Cardiovasc. Surg., 75:405, 1978.
3. Braimbridge, M. V., Chayen, J., Bitensky, L., et al: Cold Cardioplegia or Continuous Coronary Perfusion? J. Thorac. Cardiovasc. Surg., 74:900, 1977.
4. Bretschneider, H. J., Hubner, G., Knoll, D., et al.: Myocardial Resistance and Tolerance to Ischemia: Physiological and Biochemical Basis. J. Cardiovasc. Surg., 16:241, 1975.
5. Buckberg, G. D.: Left Ventricular Subendocardial Necrosis (Collective Review). Ann. Thorac. Surg., 24:379, 1977.
6. Buckberg, G. D.: The Importance of Venting the Left Ventricle. Ann. Thorac. Surg., 20:488, 1975.
7. Clark, R. E., Ferguson, T. B., West, P. N., et al.: Pharmacological Preservation of the Ischemic Heart. Ann. Thorac. Surg., 24:307, 1977.
8. Cooley, D. A., Reul, G. J. and Wukasch, D. C.: Ischemic Contracture of the Heart: "Stone Heart." Am. J. Cardiol., 29:575, 1972.
9. Ellis, R. J., Pryor, W. and Ebert, P. A.: Advantages of Potassium Cardioplegia and Perfusion Hypothermia in Left Ventricular Hypertrophy. Ann. Thorac. Surg., 24:299, 1977.
10. Fishman, N. H., Youker, J. E. and Roe, B. B.: Mechanical Injury to the Coronary Arteries during Operative Cannulation. Am. Heart J., 75:26, 1968.
11. Follette, D., Fey, K., Mulder, D., et al.: Prolonged Safe Aortic Clamping By Combining Membrane Stabilization, Multidose Cardioplegia and Appropriate pH reperfusion. J. Thorac. Cardiovasc. Surg., 74:682, 1977.
12. Fuhrman, G. J., Fuhrman, M. A. and Field, J.: Metabolism of Rat Heart Slices, With Special Reference to Effects of Temperature and Anoxia. Am. J. Physiol., 163:642, 1950.
13. Gay, W. A. and Ebert, P. A.: Functional, Metabolic and Morphologic Effects Of Potassium-Induced Cardioplegia. Surgery, 74:284, 1973.
14. Greenberg, J. J. and Edmunds, L. H.: Effect of Myocardial Ischemia at Varying Temperatures on Left Ventricular Function and Tissue Oxygen Tension. J. Thorac. Cardiovasc. Surg., 42:84, 1961.
15. Hearse, D. J., Steward, D. A. and Braimbridge, M. V.: Hypothermia Arrest and Potassium Arrest, Metabolic and Myocardial Protection During Elective Cardiac Arrest. Circ. Res., 36:481, 1975.
16. Hottenrott, C. E., Towers, B., Kurkji, H. J., et al.: The Hazard of Ventricular Fibrillation in Hypertrophied Ventricles During Cardiopulmonary Bypass. J. Thorac. Cardiovasc. Surg., 66: 742, 1973.
17. Kirsch, U., Rodewald, G. and Kolmar, P.: Induced Ischemic Arrest: Clinical Experience with Cardioplegia in Open-Heart Surgery. J. Thorac. Cardiovasc. Surg., 63:121, 1972.
18. MacGregor, D. C., Wilson, G. J., Tanaka, S., et al.: Ischemic Contracture of the Left Ventricle, Production and Prevention. J. Thorac. Cardiovasc. Surg., 70:945, 1975.
19. Miller, D. W., Jr., Hessel, F. A., II, Wintersheid, L. C., et al.: Current Practice of Coronary Artery Bypass Surgery, Results of a National Survey. J. Thorac. Cardiovasc. Surg., 73:26, 1968.
20. Okies, J. E., Phillips, S. J., Crenshaw, R. and Starr, A.: The "No-Vent" Technique of Coronary Artery Bypass, (Abs.), Year Book of Cardiology. 1976, 287–289.
21. Ries, R. L., Cohn, L. H. and Morrow, A.: Effects of Induced Ventricular Fibrillation on Ventricular Performance and Cardiac Metabolism. Circulation, 35 and 36 Suppl. 1:234, 1967.
22. Robicsek, F., Tam, W., Daugherty, H. K., et al.: Myocardial Protection During Open-Heart Surgery: Coronary perfusion versus Topical Cardiac Hypothermia. Ann. Thorac. Surg., 10:340, 1970.
23. Roe, B. B., Hutchinson, J. C., Fishman, N. F., et al.: Myocardial Protection with Cold, Ischemic, Potassium-Induced Cardioplegia. J. Thorac. Cardiovasc. Surg., 73:366, 1977.
24. Shumway, N. E. and Lower, R. R.: Topical Cardiac Hypothermia for Extended Periods of Anoxic Arrest. Surg. Forum, 10:563, 1960.
25. Stemmer, E. A., McCard, P., Stanton, W. W., Jr., et al.: Functional and Structural Alterations in the Myocardium During Aortic Cross-Clamping. J. Thorac. Cardiovasc. Surg., 66:754, 1973.
26. Stiles, Q. R., Hughs, R. K. and Lindesmith, G. G.: Effectiveness of Topical Cardiac Hypothermia. J. Thorac. Cardiovasc. Surg., 73:366, 1977.
27. Stinson, E. B.: Myocardial Preservation: Cardiac Surgery (Post graduate Course) ACS 63rd Congress, 19, 1977.
28. Todd, G. J. and Tyers, G. F. O.: Amelioration of the Effects of Ischemic Cardiac Arrest by the Intracoronary Administration of Cardioplegia Solutions. Circulation, 52:1111, 1975.
29. Urschel, H. C. and Greenberg, J. J.: Cardioplegia and Hypothermia: Differential Hypothermic Cardioplegia. Surg. Forum, 10:506, 1960.

Seeding Arterial Prostheses with Vascular Endothelium

The Nature of the Lining

MALCOLM B. HERRING, M.D., RUSSELL DILLEY, M.D., RALPH A. JERSILD, JR., PH.D., LAURENCE BOXER, M.D.,
AUSTIN GARDNER, M.D., JOHN GLOVER, M.D.

Arterial prostheses seeded with autogenous vascular endothelium demonstrate a well-organized, cellular, inner lining. To determine the nature of the lining cells, six animals underwent replacement of the infrarenal aorta with Dacron® prostheses. During the preparation of three such grafts, endothelium was scraped from the saphenous vein with a steel wool pledget, suspended in chilled Sack's solution, and mixed with blood used to preclot the graft. This suspension was omitted from the three control grafts. After six weeks, the grafts were removed, rinsed and examined. Fluorescent Factor VIII related antigen (F VIII-RA) strongly stained the lining cells. Silver nitrate Haütchen and electron microscopy preparations revealed a lining pattern characteristic of vascular endothelium. Endothelial cell-specific Weibel-Palade bodies were identified in the lining cell cytoplasm. Masson's trichrome staining revealed a relatively collagen-poor connective tissue within the seeded fabric. Transmission electron microscopy disclosed vascular smooth muscle cells between the seeded graft fabric and the lining cells. Vasa vasorum, arising from the outer capsule, penetrated the fabric to supply the inner capsules of the seeded grafts. It is concluded that the cells lining seeded canine arterial prostheses are true vascular endothelium supported by vascular smooth muscle cells, that the lining contains minimal connective tissue, and that vasa vasorum develop. Unseeded control grafts lacked these features.

SINGLE-STAGED CANINE endothelial seeding results in a well-organized, cellular graft lining.[8] The lining cells appear to be endothelium; however, fibroblasts are frequent histologic counterfeits.[7] Fibroblasts ultimately line porous grafts in humans and dogs which have been prepared by customary clinical techniques.[1,2,4,5–7,9,14,15] This study will identify and describe the organization of cells lining "seeded" and control prostheses.

Materials and Methods

Six healthy, anesthetized mongrel dogs, weighing 14 kg or more, underwent aseptic replacement of the infrarenal aorta using 6 mm knitted Dacron® arterial grafts. The grafts were preclotted by the Sauvage technique.[13] Each dog received systemic heparin, 100 units/kg prior to aortic clamping and interpolation of the graft. In three dogs, a suspension of endothelial cells was added to the blood used for preclotting. The suspension of endothelial cells was added to the blood used for preclotting. The cell suspension was prepared in the following way. The right saphenous vein was exposed through a longitudinal incision in the groin. The branches were ligated. Ligatures were placed 10–15 cm apart on the vein. The vein was distended with chilled Sack's solution and opened longitudinally. A #2 steel wool pledget was used to scrape the lining cells from the vein. The cells which were caught in the steel wool pledget were then rinsed into 2 ml of chilled Sack's solution[12] which comprised the suspension. In the remaining three dogs this suspension was omitted from the preclotting procedure. The grafts were removed six weeks after implantation, rinsed and studied.

Silver nitrate Haütchen preparations were made by placing a portion of each graft in 0.3% silver nitrate solution immediately after extraction. After five minutes it was removed, rinsed with normal saline, and exposed to the light for 10–20 minutes. It was then placed in 10% buffered formalin until further preparations were made. The grafts were removed from formalin solution and gently patted dry with lint free paper. A scalpel was used to skive the luminal-most layer from the graft. This layer was sandwiched between squares of cellulose polyacetate membrane (Sepraphore III-Gelman) and placed on a microscope cover slip. The materials were

From the Department of Surgery, St. Vincent Hospital,
Wishard Memorial Hospital and The Departments of
Anatomy and Pediatrics, Indiana University School
of Medicine, Indianapolis, Indiana

Reprint requests: Malcolm B. Herring, M.D., 8402 Harcourt Road, Suite 802, Indianapolis, Indiana 46260.

Submitted for publication: August 23, 1978.

0003-4932/79/0700/0084 $00.85 © J. B. Lippincott Company

allowed to dry. The paper was cleared with xylol, and mounted on a microscope slide with Permount.

Each graft, plus control sections of each dog's saphenous vein, abdominal, aorta and peritoneum were examined by immunofluorescent staining of F VIII-RA. A small midgraft section was removed from the anesthetized animal and placed immediately in chilled phosphate buffered saline (PBS). The inner capsule (the tissue forming between the graft and the flowing blood) was dissected from the graft fabric. Frozen microscopic sections were made and the slides stored at −20°. The slides were immersed in acetone for ten minutes and fixed by air drying. A drop of 1:16 dilution of rabbit anti-canine Factor VIII related antibody (F VIII-Ab) was spread over the tissue surface and incubated for 30 minutes at room temperature, changing the PBS once. The specimen was covered with a 1:250 dilution of rhodamine-conjugated, goat antirabbit globulin for 30 minutes at room temperature, washed again, and covered with a 10% glycerol in PBS and a cover slip. Specimens were studied with a reflected Zeiss epi-illumination system, using a 50 watt mercury vapor lamp, 510 LP and KP 560 exciter filters, and 580 LP barrier filter.

Formalin preserved graft specimens were embedded in JB-4 resin (Polyscience). Microscopic sections, four to seven microns in thickness, were prepared and stained by hematoxylin and eosin, Masson's trichrome, and Verhoeff's elastin stains. The vasa vasorum were studied using serial hematoxylin and eosin sections.

A portion of seeded midgraft was prepared for transmission electron microscopy. Immediately after removal, a small segment of the graft was placed in chilled 3% glutaraldehyde, buffered to pH 7.4 with 0.1 M sodium cacodylate, and fixed at 5° for 16 hours. Secondary fixation was in 1% cacodylate-buffered OsO_4 for one hour, followed by ethanol dehydration and epon embedment. The sections were stained with uranyl acetate and lead citrate.

Results

By gross observation, the seeded grafts were healed over most of the luminal surface. Hematoxylin and eosin microscopic sections disclosed flattened lining cells, a well-organized, cellular sublining and the development of vasa vasorum. The unseeded controls[8] shared none of these components.

The vasa vasorum extended into the linear capsule (Fig. 1) to within 500 microns of the lumen. The major vasa channels, measuring 10–40 microns in diameter, coursed circumferentially. Adjacent smooth muscle cell axes were also oriented more circumferentially at this level in the inner capsule. Outer capsule channels were similar in size and direction and were located at the same distance from the lumen. Many capillary-sized channels connected the inner capsule network with the outer capsule vasa vasorum. Larger connections were seen passing through so-called "tufts" of tissue between the yarn bundles (Fig. 2). The outer connec-

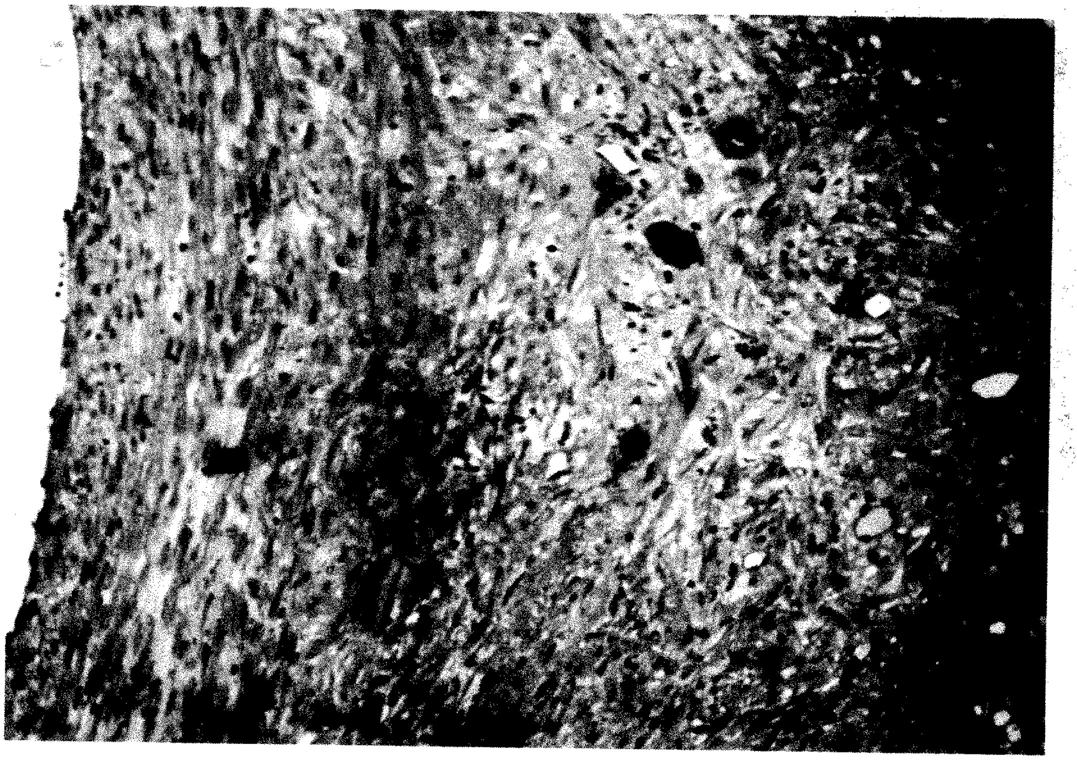


FIG. 1. Hematoxylin and eosin photomicrograph of a seeded prosthesis. The vasa vasorum extend into the inner capsule. Smooth muscle cell axial orientation is longitudinal to within 400 microns of the lumen, except when limited by the graft fabric. Deeper layers show more cells with a circumferential axial orientation.

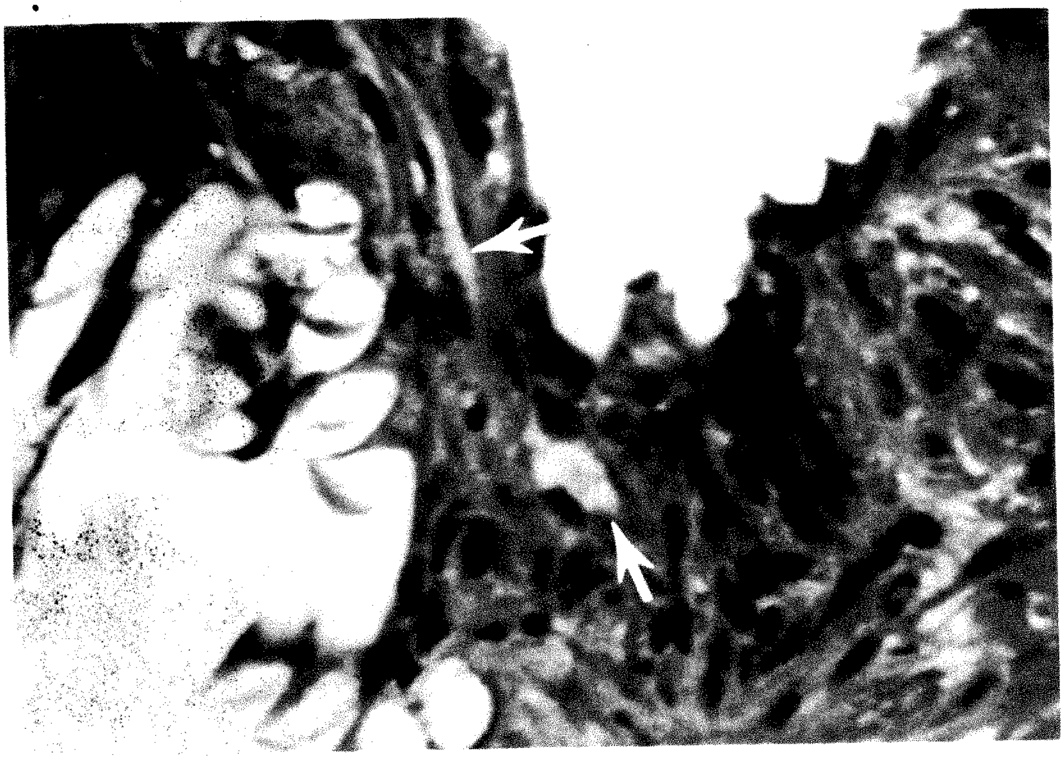


FIG. 2. Hematoxylin and eosin photomicrograph of a seeded prosthesis. Vascular communications pass from the inner to the outer capsules through so-called "tufts" of tissue between the yarn bundles.

tions communicated with larger vascular channels which developed near the perigraft fat and coursed in the direction of graft flow (Fig. 3). At no point could any major communication of the vasa with the graft lumen be detected.

The smooth muscle cell orientation reflected the pattern seen in hematoxylin and eosin sections of normal vessels. The longitudinal cell axis was aligned with the direction of graft flow near the lumen to about 350–400 microns in depth (Fig. 1). In the areas where the graft fabric was closer than 350 to 400 microns from the lumen, the depth to which this cellular orientation extended was limited by the fabric. Deep layers were less consistent, including more cells whose axes were perpendicular to the direction of blood flow. In the outer capsule, smooth muscle cells predominated but were somewhat more closely organized.

Masson's trichrome staining revealed considerably less connective tissue staining in seeded grafts (Fig. 4) as compared to unseeded (Fig. 5). Elastin was not apparent in any of the graft sections but was readily stained on aortic sections prepared in the same fashion.

Silver nitrate Haütchen preparations revealed the surface to be covered with a monolayer of cells stained around their entire perimeter (Fig. 6). In contrast, no cellular pattern could be detected on unseeded graft surfaces. F VIII-RA studies revealed a strong fluorescent staining by the lining cells in the seeded grafts (Fig. 7), abdominal aortas, and saphenous veins but not in the unseeded grafts and peritoneum. No tissue treated with normal rabbit serum (instead of the antiserum to canine F VIII-RA) showed any specific fluorescence.

Electron microscopic sections showed the lining of the graft to be composed of a continuous sheet of highly flattened cells. A thickened cytoplasmic area around the nucleus contained the greatest organellar development—including a prominent rough endoplasmic reticulum, a well-developed juxtanuclear Golgi apparatus, numerous mitochondria, and scattered, dense

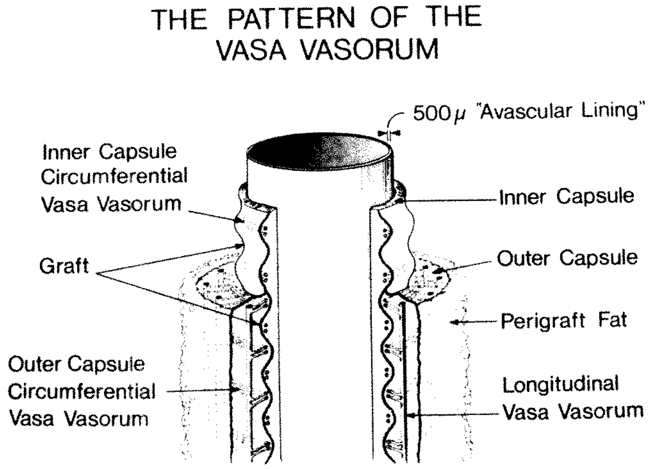

THE PATTERN OF THE
VASA VASORUM
500μ "Avascular Lining"
Inner Capsule Circumferential Vasa Vasorum
Inner Capsule
Graft
Outer Capsule
Perigraft Fat
Outer Capsule Circumferential Vasa Vasorum
Longitudinal Vasa Vasorum

FIG. 3. Diagram of the vasa vasorum anatomy in seeded prostheses. The innermost 500 microns is relatively avascular. Vasa networks course circumferentially in the inner and outer capsules. Longitudinal vasa vasorum are seen in the outer capsule near the perigraft fat.

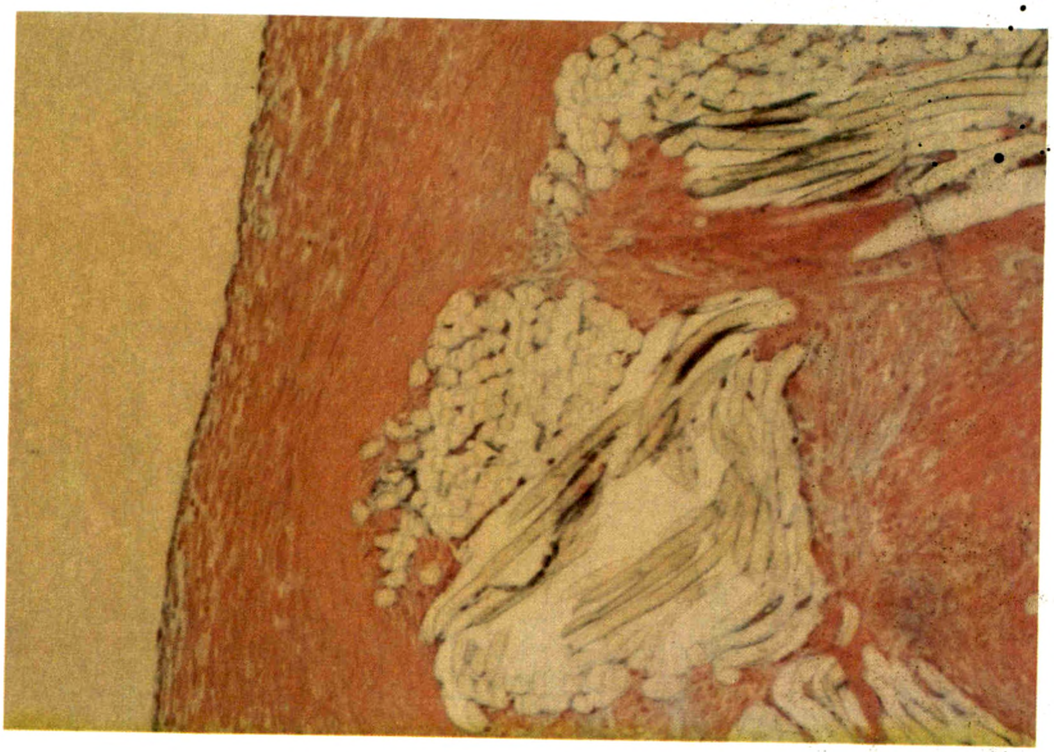


FIG. 4. Masson's trichrome photomicrograph of a seeded arterial prosthesis. Little blue-staining connective tissue is seen and only in areas within one to two microns of the Dacron fabric, the vicinity of the vasa vasorum and the perigraft fat.

and multivesicular bodies (Figs. 8 and 9). Cytoplasmic filaments were frequently observed throughout the entire cell. These often were aggregated into bundles containing areas of increased density along the basal surface of the cell (Fig. 9). Weibel-Palade granules were observed and widely disbursed throughout the lining cells (Fig. 10). Pinocytotic vesicles were numerous (Fig. 10). The cell surface displayed occasional luminal and basal projections. The later were observed at times to contact the surface of the under-

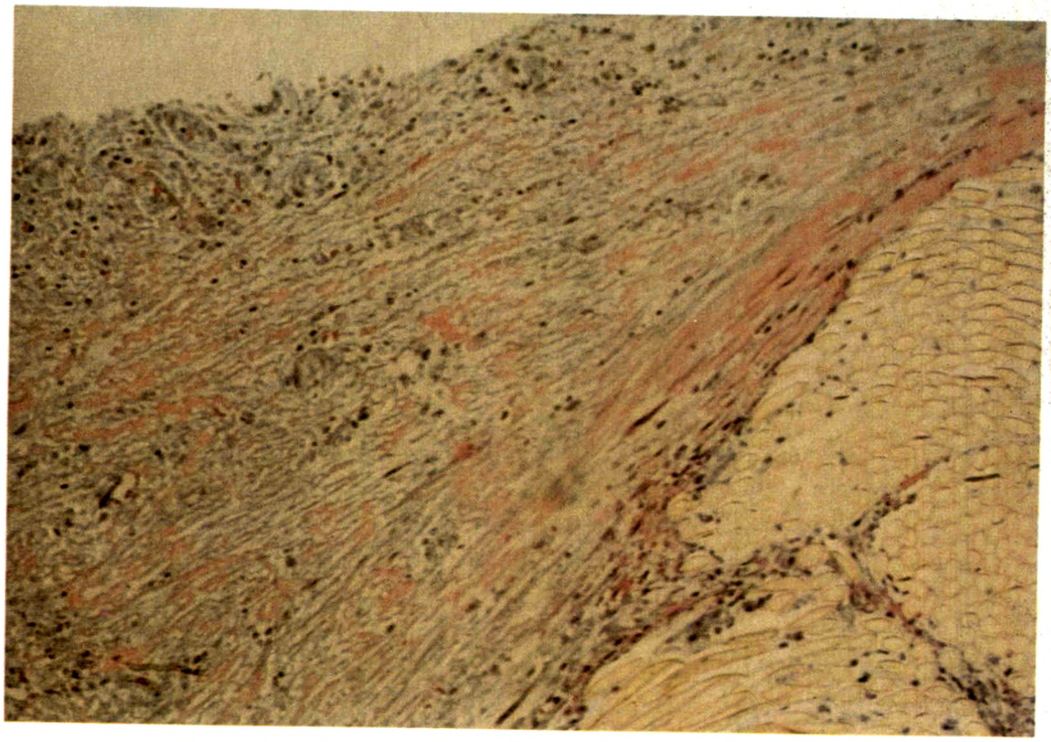


FIG. 5. Masson's trichrome photomicrograph of an unseeded prosthesis. Blue-staining connective tissue is seen throughout the inner and outer capsules of the graft.

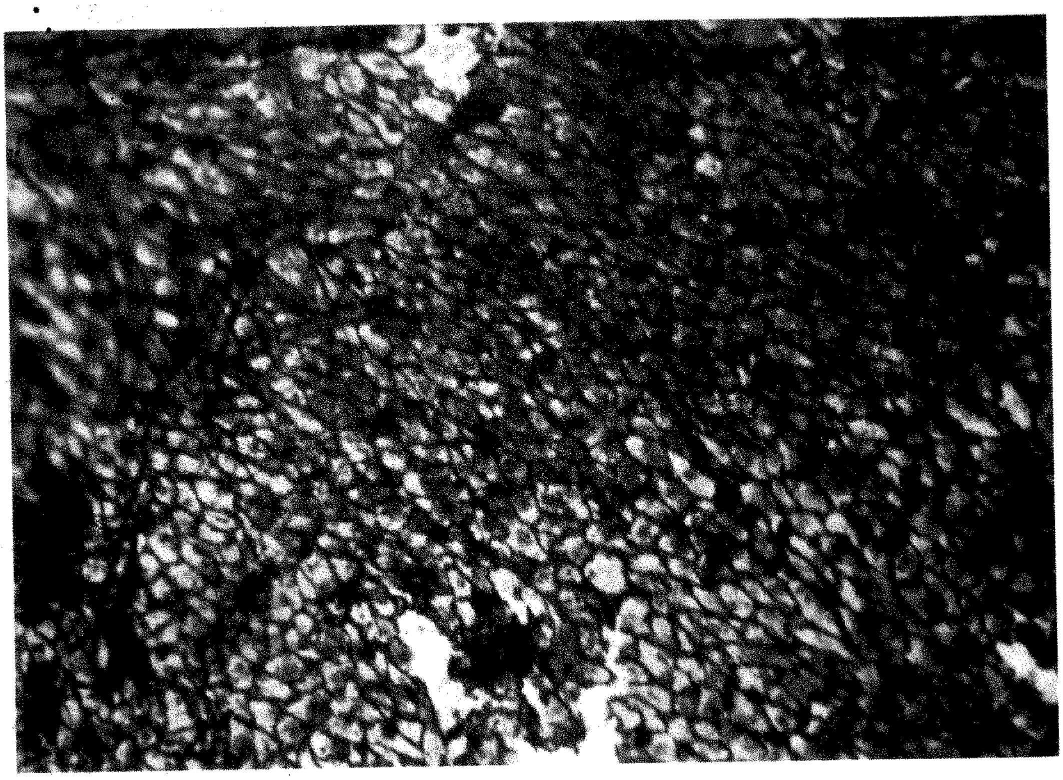


FIG. 6. Silver nitrate Haütchen preparation of a seeded arterial prosthesis. A characteristic endothelial monolayer pattern is seen, the cells are polygonal and stained around their entire perimeter.

lying smooth muscle cells. The lateral boundaries typically displayed complex interdigitations with adjacent cells. Junctional specializations of the cell membrane were not observed except for occasional desmosomes. A basement membrane was indistinct or lacking.

The underlying stroma appeared largely as granular and fibrillar deposits in an amorphous substance of

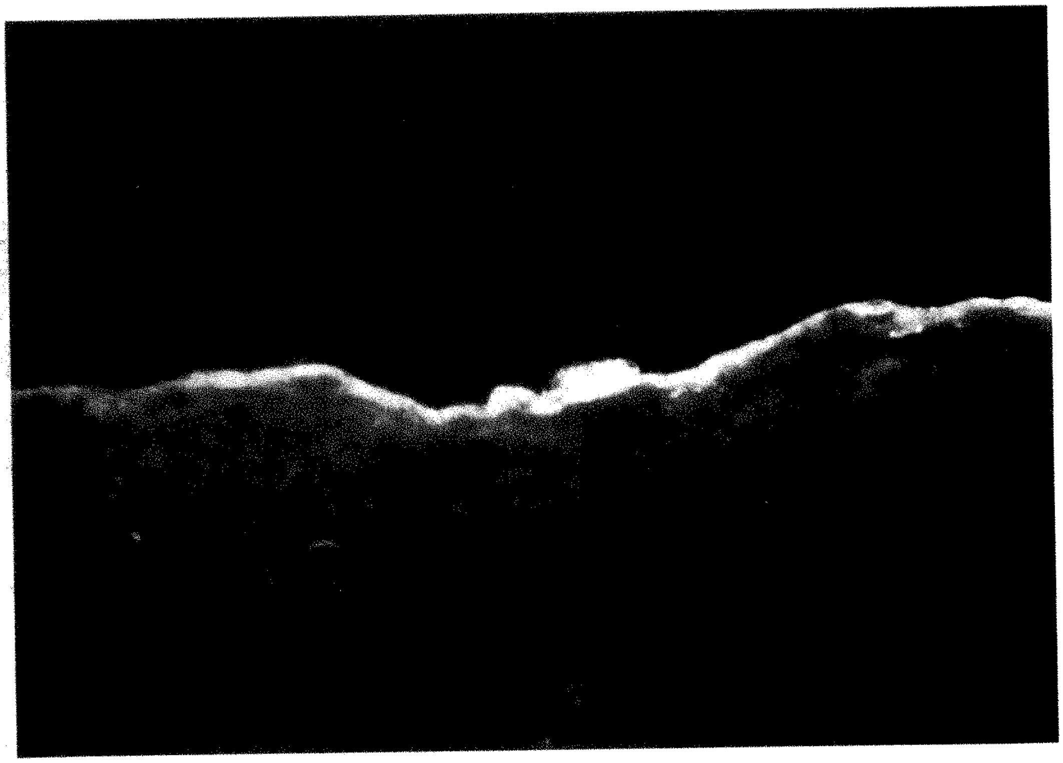


FIG. 7. Fluorescent F VIII-RA preparation in a seeded arterial prosthesis. Strong fluorescent staining by the lining cells is noted.

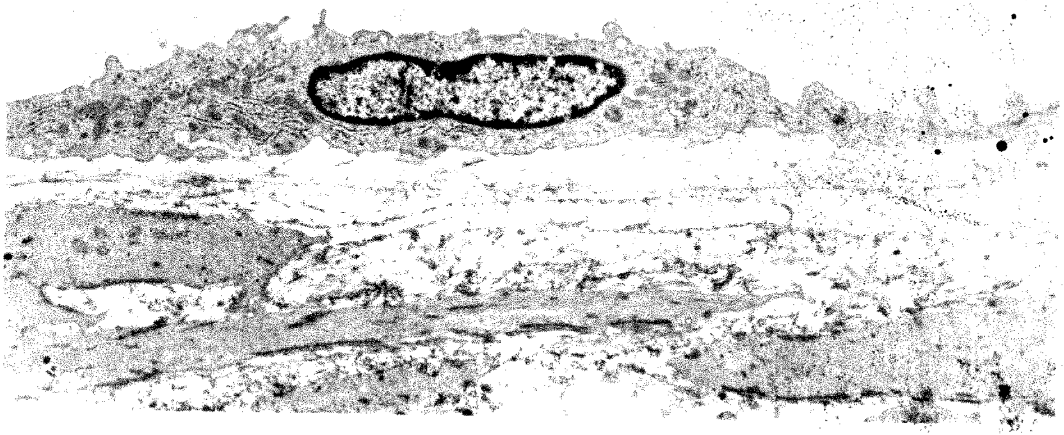


FIG. 8. Electron micrograph showing a characteristic endothelial cell (top) and portions of some underlying smooth muscle cells. A loosely knit network of fine filaments is suspended in the ground substance between cells (×9,500).

low electron density. Smooth muscle cells oriented along the graft flow axis were loosely organized in the subendothelial space (Fig. 8). An occasional smooth muscle cell was observed on the luminal surface. These cells remained thick over much of their length and retained the main cytoplasmic features characteristic of the underlying smooth muscle cells.

Discussion

The vasa vasorum which developed following single-staged endothelial seeding of canine arterial prostheses compare with the vasa vasorum found in the natural canine abdominal aorta. Both have major communications with longitudinal vasa channels near the perivascular fat.[3] From these larger channels the network extends toward the lumen to within about 500 microns from the blood flow surface. The vasa tend to course along the graft fabric and communicate with the inner capsule network via smaller channels between the yarn bundles. The channels in the inner and outer capsules course circumferentially, following the graft crimp. What effect removing the graft crimp would have on this orientation remains the subject of future investigations.

Endothelial cells were seeded during graft preparation into a matrix of blood clot, supported by the graft fabric. It is unlikely that the lining endothelium originated from cells in the new vasa vasorum, since no communication between the vasa and the graft lumen could be identified. The lining endothelium appears to develop from endothelial "seeds" near the lumen.

As typifies would healing, the new vasa vasorum develop from extensions of adjacent blood vessels. The conditions in the seeded grafts which permit them to develop are unknown. Possibly, endothelial "seeds" form an anlage for the early development of vasa vasorum.

The presence of vasa vasorum implies a nutritional advantage for the linings of arterial prostheses prepared in this manner. Such nutrition permits regeneration of lining cell elements following injury. This contrasts to the limited repair capacity described by Wesolowski[15]

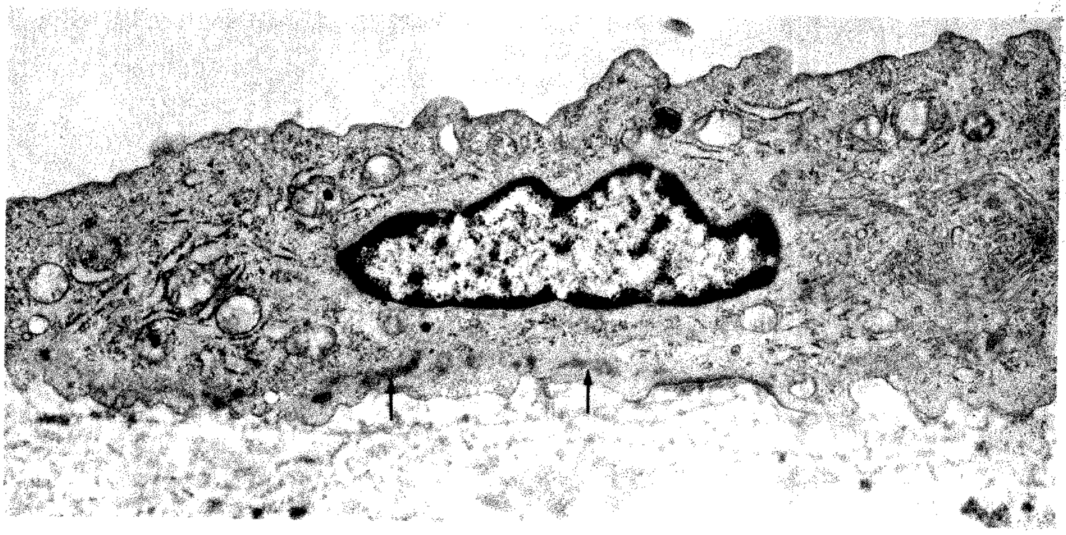


FIG. 9. Portion of an endothelial lining cell in the region of the nucleus with a typical display of rough endoplasmic reticulum, mitochondria and Golgi apparatus (right of nucleus). In this cell, cytoplasmic filaments are distributed along the basal surface with locally dense concentrations (arrows) (×14,000).

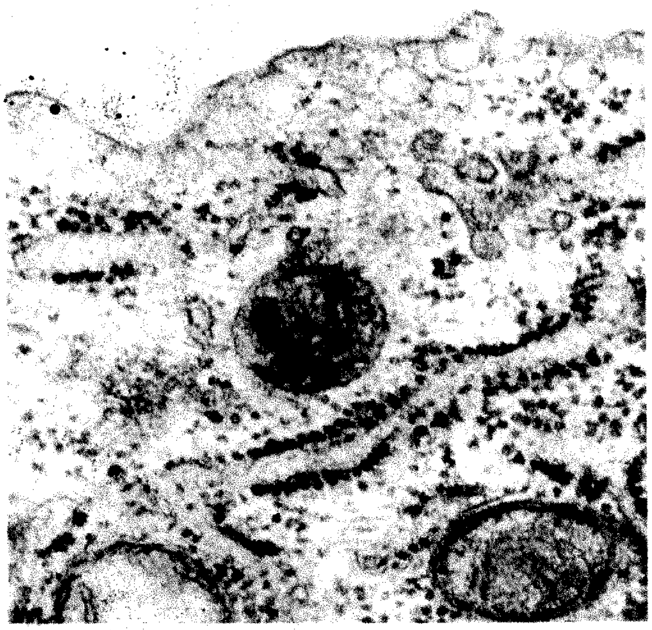


FIG. 10. Highly magnified portion of an endothelial lining cell along the luminal surface. A Weibel-Palade granule is in the center of the micrograph. Pinocytotic vesicles border the luminal surface (×67,000).

following fibroblastic ingrowth. Removal of subintimal macromolecules by the vasa vasorum theoretically would inhibit the development of atheroma in the graft.

The sublining cells were predominately vascular smooth muscle cells and only occasionally fibroblasts. Their axial orientation was similar to natural arterial smooth muscle. The deep layer was oriented more transversely.[11] Vascular smooth muscle may ultimately prove indispensable to the support of endothelial lining cells. In addition, the contractile muscle may help seal the prosthesis should it be punctured for dialysis or some other reason. More importantly, the proliferation of smooth muscle cells supplants fibroblastic ingrowth. This, in turn, may limit the formation of thrombogenic collagen. The deposition and maturation of collagen in the inner and outer capsules and in the fabric eventuates in ever increasing graft stiffness. The elastic qualities of the prosthesis at implantation may be extended into the later phases of healing by a more distensible smooth muscle lining.

No elastin was observed in the "seeded" prosthesis lining. This might reflect the paucity of fibroblasts. Yet, elastin was similarly absent in the fibroblast-lined, "unseeded" prostheses. It may be that pulsatile vessel distention stimulates elastin formation and that the non-distensible Dacron graft may have precluded such stimulation.

The characteristic appearance of silver nitrate Haütchen preparations, the strong staining of F VIII-RA and the presence of endothelial cell-specific Weibel-Palade bodies on transmission electron microscopy serve to identify the lining cells, unequivocally, as true vascular endothelium. The capacity of a natural endothelial cell lining to regenerate, resist thrombosis and possibly resist bacterial invation[10] makes this an inviting technique for future laboratory and clinical investigation.

We conclude from this study that the linings of healed arterial prostheses, prepared in dogs by the single-staged technique, were comprised of true vascular endothelium supported by vascular smooth muscle and vasa vasorum.

Acknowledgments

We wish to thank Lilly Pharmaceuticals, Dow Pharmaceuticals and St. Vincent Hospital, Foundation, Indianapolis, Indiana for their financial support; Roger E. Benson and W. Jean Dodds, Albany, New York for supplying rabbit anticanine Factor-VIII antibody; and U.S.C.I. Div. of C. R. Bard, Billerica, Mass. for supplying Dacron prostheses.

References

1. Berger, K., Sauvage, L. R., Rao, A. M. and Wood, S. J.: Healing of Arterial Prosthesis in Man, Its Incompleteness. Ann. Surg., 175:118, 1972.
2. Brais, M. P. and Braunwald, N. S.: Tissue Acceptance of Materials Implanted Within the Circulatory System. Arch. Surg., 109:351, 1974.
3. Brook, W. H.: Vase Vasorum of Veins in Dog and Man. Angiology, 28:351, 1977.
4. DeBakey, M. E., Jordan, G. L., Jr., Abbott, J. P., et al.: The fate of Dacron vascular grafts. Arch. Surg., 89:757, 1964.
5. Foster, E. D., Smith, M. R. and Dobell, A. R. C.: Thrombosis on Prosthetic Surfaces, A Review of Etiologic Factors and Preventive Measures. Can. J. Surg., 15:339, 1972.
6. Gott, V. L., Ameli, M. N., Whiffen, J. D., et al.: Newer Thromboresistant Surfaces, Evaluation of a New In Vivo Technique. Surg. Clin. North Am., 47:1443, 1967.
7. Gottlob, R.: Endothelial Regeneration, The Role of Smooth Muscle Cells, Blood Cells and Histiocytes. Prog. Biochem. Pharmacol., 14:276, 1977.
8. Herring, M. B., Gardner, A. L. and Glover, J.: A Single Staged Technique for Seeding Vascular Grafts with Autogenous Endothelium. Surgery, 84:498, 1978.
9. Lindenauer, S. M., Weber, T. R., Miller, T. A., et al.: Velour Vascular Prostheses. Trans. Am. Soc. Artif. Intern. Organs, 20A:317, 1974.
10. Moore, W., Rosson, C. T., Hall, A. D. and Thomas, A. N.: Transient Bacteremia, A Cause of Infection in Prosthetic Vascular Grafts. Am. J. Surg., 117:342, 1969.
11. Rhodin, J. A. G.: Histology, A Text and Atlas. New York, Oxford University Press, 1974, p. 340.
12. Sacks, S. A., Petritsch, P. H. and Kaufman, J. J.: Canine Kidney Preservation Using a New Perfusate. Lancet, 1024, 1973.
13. Sauvage, R., Berger, K., Wood, S. J., et al.: Healing of Arterial Prostheses, Goal of Design and Clinical Use. Reconstr. Cardiovasc. Res. Center, 1976.
14. Stewart, C. J., Essa, N., Chang, K. H. Y. and Reichele, F. A.: A Scanning and Transmission Electron Microscope Study of a Luminal Coating on Dacron Prostheses in the Canine Thoracic Aorta. J. Lab. Clin. Med., 85:208, 1975.
15. Weslowski, S. A., Fries, C. C., Martinez, A. and McMahon, J. D.: Arterial Prosthetic Materials. Ann. N. Y. Acad. Sci., 146:325, 1968.

OSTO ERATIVE PAI

prompt narcotic/analgesic relief without A.P.C.

The principal analgesic ingredient, oxycodone, is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine. The analgesic effect of oxycodone begins within 10 to 15 minutes after oral administration, peaks at 45 minutes, and persists for 3 to 6 hours.[†] Acetaminophen, a non-narcotic analgesic, complements the pain relief provided by oxycodone.

Summary of Prescribing Information

Contraindications: Hypersensitivity to oxycodone or acetaminophen.

Warnings: *Drug dependence:* Oxycodone can produce drug dependence of the morphine type and may be abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration; prescribe and administer with same caution appropriate to other oral narcotic-containing medications. Subject to the Federal Controlled Substances Act.

Usage in ambulatory patients: Caution patients that oxycodone may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

Interaction with other Central Nervous System depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) with TYLOX capsules may exhibit additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy: Safe use not established. Should not be used in pregnant women unless potential benefits outweigh possible hazards.

Usage in children: Should not be administered to children.

Precautions: *Head injury and increased intracranial pressure:* The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: TYLOX capsules or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.

Special risk patients: Administer with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Adverse Reactions: *Most frequent:* Lightheadedness, dizziness, sedation, nausea and vomiting; more prominent in ambulatory than non-ambulatory patients; some of these reactions may be alleviated if the patient lies down. *Others:* euphoria, dysphoria, constipation, skin rash and pruritus.

Dosage and Administration: Dosage should be adjusted according to severity of pain and response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. TYLOX capsules are given orally. Usual adult dose is one capsule every 6 hours as needed for pain.

Drug Interactions: CNS depressant effects may be additive with that of other CNS depressants. See Warnings.

Caution: Federal law prohibits dispensing without prescription.

For information on symptoms/treatment of overdosage, see full prescribing information.

Full directions for use should be read before administering or prescribing.

[†] Halpern, L.M., and Bonica, J.J., "Analgesics," in Modell, W., ed. Drugs of Choice 1976-1977, St. Louis, The C.V. Mosby Co., 1976, p. 213. 0775

TYLOX® CII

CAPSULES

oxycodone HCl* 4.5 mg,
oxycodone terephthalate* 0.38 mg,
acetaminophen 500 mg

***Warning:** May be habit forming.

McNEIL

McNeil Laboratories, McNEILAB, Inc., Fort Washington, PA 19034

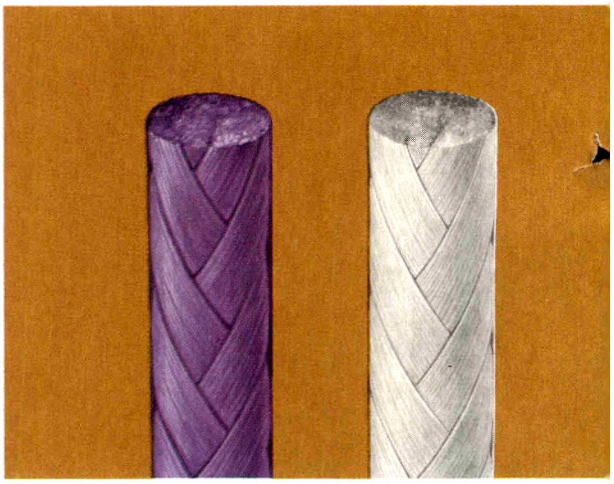
© McN 1978

ETHICON DOES IT AGAIN

VICRYL* (Polyglactin 910) suture

Improved braided construction results in:

Superior smoothness
Better knot security
Improved handling characteristics
—In addition to the other benefits VICRYL suture is known for. Available dyed and undyed on a wide variety of needles.



Available braided, dyed and undyed.

ETHICON
the closing word

Revised 6 77

VICRYL*
(Polyglactin 910) suture

COMPLETE PRODUCT INFORMATION

VICRYL* (Polyglactin 910)
Synthetic Absorbable Suture

DESCRIPTION VICRYL (polyglactin 910) synthetic absorbable suture is prepared from a copolymer of glycolide and lactide. These substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C\,H_2O\,)m(C\,H_4O\,)n$

VICRYL sutures are sterile, inert, nonantigenic, nonpyrogenic, and elicit only a mild tissue reaction during absorption. The braided and monofilament sutures are colored violet to enhance visibility in tissue. The braided suture is also available undyed (natural)

ACTIONS Two important characteristics describe the *in vivo* behavior of absorbable sutures: first, tensile strength retention, and second, the absorption rate (loss of mass)

Subcutaneous tissue implantation studies of VICRYL suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained

Intramuscular implantation studies in rats show that the absorption of VICRYL suture is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days

INDICATIONS VICRYL synthetic absorbable suture is intended for use as an absorbable suture or ligature

CONTRAINDICATIONS This suture, being absorbable, should not be used where extended approximation of tissues under stress is required

WARNINGS The safety and effectiveness of VICRYL (polyglactin 910) suture in neural tissue, and in cardiovascular surgery have not been established

Under certain circumstances, notably orthopedic procedures, immobilization by external support may be employed at the discretion of the surgeon

Do not resterilize

PRECAUTIONS VICRYL suture knots must be properly placed to be secure. Place the first throw in precise position for the final knot, using a double loop; tie the second throw square, using horizontal tension; additional throws are advisable

Skin and conjunctival sutures remaining in place longer than 7 days may cause localized irritation and should be removed as indicated

Acceptable surgical practice must be followed with respect to drainage and closure of infected wounds

ADVERSE REACTIONS Reactions reported in clinical trials which may have been suture related have been minimal. These include skin redness and induration; rare instances of hemorrhage, anastomotic leakage, wound separation in the eye, and abscesses

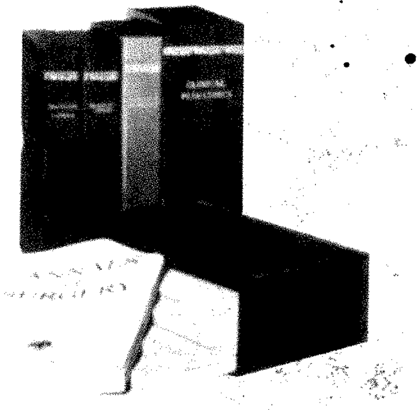
DOSAGE AND ADMINISTRATION Use as required per operation

HOW SUPPLIED VICRYL sutures are available sterile, as braided dyed (violet) and undyed (natural) strands in sizes 3 to 8-0, in a variety of lengths, with and without needles, and on LIGAPAK ligating reels. VICRYL sutures, monofilament, dyed (violet) are available in sizes 9-0 and 10-0 in a variety of lengths with needles

Also available in sizes 1 to 4-0 attached to CONTROL RELEASE needles

Trademark

ETHICON



PRESERVE and PROTECT
YOUR COPIES OF
ANNALS of SURGERY

Now, your journals can become a handsome addition to your professional library.

These file boxes are designed and custom-made to keep your copies orderly, readily accessible and clean.

Durable book-binder's board covered with scuff-resistant, washable Leathertex. Lettering embossed in 23-Karat gold leaf.

Jesse Jones Box Corp. (since 1843)
Dep't. JBLA—Phila., Pa. 19141

Gentlemen: Kindly send me:

Reasonably priced, too. Only $4.95 ea. ☐
3 for $14.00 ☐ 6 for $24.00 ☐

Add $1.00 postage per file for orders outside the U.S.

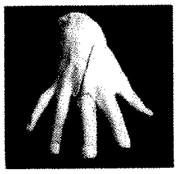
☐ Check enclosed (Make check payable to: Jesse Jones Box Corp., Box 5120, Phila., Pa. 19141)

Name ____________________
Address ____________________
City/State/Zip ____________________

Shipped postpaid U.S. only. Satisfaction unconditionally guaranteed or your money back.

See below for important product information concerning warnings, adverse reactions, patient selection and prescribing and precautionary recommendations.

Let the healing begin in pain-free comfort



Marcaine® hydrochloride
brand of
bupivacaine hydrochloride
with or without epinephrine 1:200,000

Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

Allergic reactions, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

References:

1. Moore DC, Bridenbaugh LD, Thompson GE: Bupivacaine hydrochloride: a summary of investigational use in 3,274 cases. *Anesth Analg* 50: 856-872, 1971.
2. Moore DC, Bridenbaugh LD, Thompson GE, et al: Bupivacaine: a review of 11,080 cases. *Anesth Analg* 57:42-53, 1978.

BREON
BREON LABORATORIES, INC.
90 Park Avenue, New York, N.Y. 10016

FORMULA

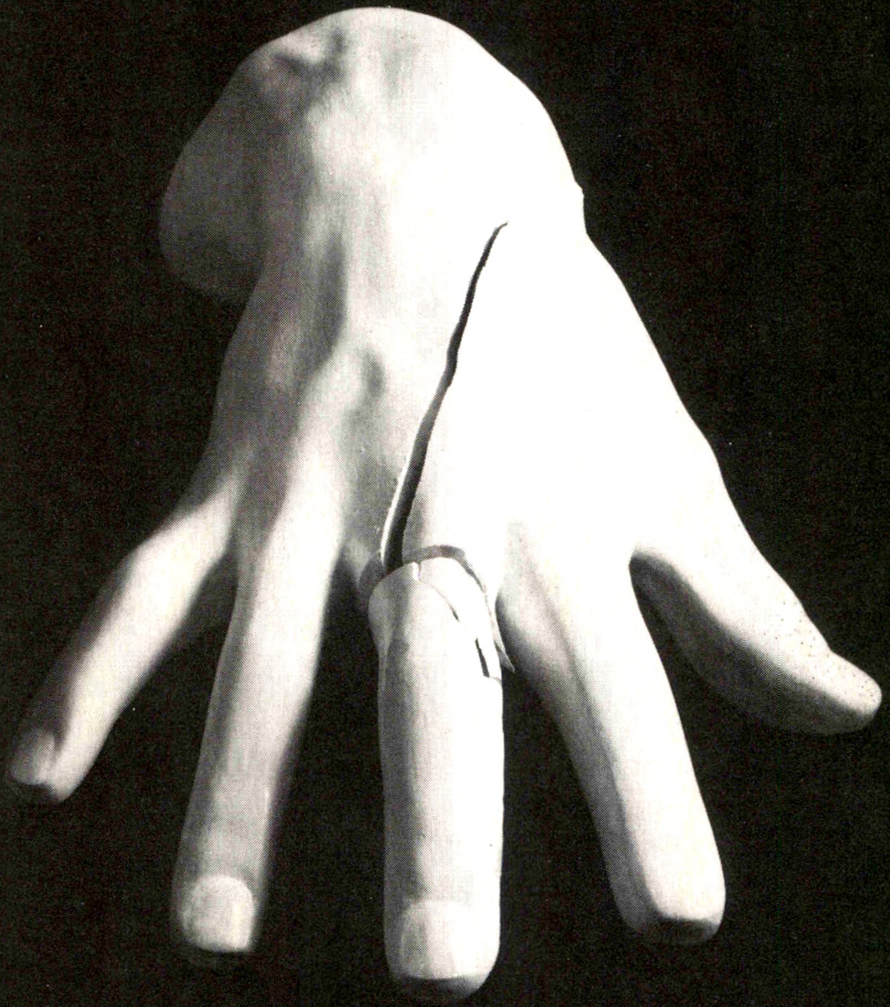
PRODUCT IDENTIFICATION			MULTIPLE DOSE VIAL						SINGLE DOSE AMPUL				
Marcaine HCl (brand of bupivacaine HCl) %	mg./ml.	Epinephrine* (as bitartrate) Dilution	Methylparaben mg./ml.	Sodium Bisulfite mg./ml.	Thioglycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.	Sodium Bisulfite mg./ml.	Thioglycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.
0.25	2.5	—	1	—	—	—	—	—	—	—	—	—	—
0.25	2.5	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.5	5.0	—	1	—	—	—	—	—	—	—	—	—	—
0.5	5.0	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.75	7.5	—							—	—	—	—	—
0.75	7.5	1:200,000	Not Available in Vials						.5	.001	2	.0017	0.1

Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved.

Federal law prohibits dispensing without a prescription.

Let the healing begin in pain-free comfort



Of all commonly used local anesthetics,
Marcaine® defers pain for so long,
there's significantly less need
for postoperative analgesics.[1,2]

Marcaine® hydrochloride
brand of
bupivacaine hydrochloride
with or without epinephrine 1:200,000
See adjacent page for prescribing information.

When did you last hear 'rave reviews'– for an intraperitoneal irrigation agent?

"We were satisfied that kanamycin was not only safe, but also effective in improving survival in the presence of peritoneal contamination." —Nelson, J.L., et al.: Symposium on Surgical Infections and Antibiotics, Surg. Clin. of N.A. 55:6, pages 1391-1395, (December) 1975.

"Kanamycin has been employed in 128 patients at the time of operation for intraperitoneal contamination of various types. There has been no evidence of toxicity from this use of kanamycin." —Cohn, I., Jr., and Cotlar, A.M.: Ann. Surg. 155:532 (Apr.) 1962.

"Wider usage of intraperitoneal kanamycin is advocated when intraperitoneal antibiotic therapy is indicated." —Cohn, I., Jr., and Cotlar, A.M.: Ann. Surg. 155:532 (Apr.) 1962.

"...immediate operative use of intraperitoneal antibiotic treatment has lowered the incidence of complications and mortality by 42%." —Clowes, G.H.A.: Forum on Peritonitis, Mod. Med. 40:153 (Apr. 17) 1972.

...our choice at the operating table is kanamycin..." —Clowes, G.H.A.: Forum on Peritonitis, Mod. Med. 40:153 (Apr. 17) 1972.

"Intraperitoneal kanamycin therapy is strongly advocated for any patient with peritonitis." —DiVicenti, F.C., and Cohn, I., Jr.: Am. Journ. Surg. 111:1, pages 147-153, (June) 1965.

"In peritonitis, intraperitoneal administration of kanamycin can be recommended..." —Pissiotis, C.A., et al.: Surg. Gynecol. Obstet. 134:995 (June) 1972.

Kantrex®

KANAMYCIN SULFATE

a known quantity

BRISTOL™ BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, New York 13201

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Combined Kantrex® Injection
and Pediatric Injection
(kanamycin sulfate injection)
(13) 2/28/78

For complete information, consult Official Package Circular.

WARNING:
The major toxic effect of parenterally administered kanamycin sulfate is its action on the auditory portion of the eighth nerve. High frequency deafness usually occurs first and can be detected by audiometric testing. Tinnitus or vertigo may occur and are evidence of vestibular injury and impending bilateral irreversible deafness.

In patients with impaired kidney function, the risk of severe ototoxic reactions and permanent deafness is sharply increased. In such cases, the daily dosage should be reduced and the interval between doses lengthened. If there is evidence of progressive renal dysfunction (increasing NPN, BUN, creatinine or oliguria) during therapy, audiometric tests are advised and discontinuation of the drug should be considered.

Older patients and patients receiving a total dose of more than 15 Gm. of kanamycin sulfate should be carefully observed for signs of eighth nerve damage.

Infants and children generally tolerate the drug well; and when the recommended precautions are followed, the incidence of toxic reactions is low.

Neuromuscular paralysis with respiratory depression may occur when kanamycin sulfate is administered intraperitoneally concomitantly with anesthesia and muscle-relaxing drugs. Although there have been isolated reports of respiratory depression following intraperitoneal instillation of kanamycin, there is no conclusive proof that this side effect can be produced with recommended doses of the drug

The concurrent systemic use of other ototoxic and/or nephrotoxic drugs, particularly streptomycin, polymyxin B, polymyxin E (colistin), neomycin, gentamicin, and viomycin should be avoided.

The administration of kanamycin sulfate and rapid acting diuretic agents, e.g. ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin, and mannitol (particularly when the diuretic is given intravenously) may cause irreversible deafness. Concurrent use of these agents should be avoided. (See "Adverse Reactions".)

Usage in Pregnancy
Safety of this drug in human pregnancy has not been established.

CONTRAINDICATIONS:
A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other potentially ototoxic agents may be a contraindication if effective, alternative therapy is available.

THIS DRUG IS **NOT** INDICATED IN LONG-TERM THERAPY (e.g. Tuberculosis) BECAUSE OF THE OTOTOXIC HAZARD WITH EXTENDED ADMINISTRATION.

WARNING:
See "Warning" box above.

PRECAUTIONS:
Obtain audiograms before and during therapy in patients with renal dysfunction when treatment lasts more than 5 days. Stop Kantrex if tinnitus or hearing loss occurs. Hydrate patients to prevent chemical irritation of the renal tubules. Assess renal function periodically, both before and during therapy. If signs of renal irritation occur (casts, cells, proteinuria), increase hydration and reduce the dosage or the frequency of dosage if necessary. In azotemic patients, the frequency (in hours) of doses may be obtained by multiplying the serum creatinine by 9. If azotemia or oliguria occurs, discontinue therapy. Mycotic or bacterial superinfection may occur.

ADVERSE REACTIONS:
Nephrotoxicity—albuminuria, presence of white and red cells, granular casts, azotemia and oliguria have been reported.

Ototoxicity—see box warning.

Irritation or pain at the injection site, skin rash, drug fever, headache and paresthesias.

DOSAGE AND ADMINISTRATION:
The usual dose is 7.5 mg./Kg./12 hours I.M. or I.V. The average adult dose is 1 Gm. daily. The maximum adult total daily dose should not exceed 1.5 Gm. by all routes of administration and the total amount administered should not exceed 15 Gm.

The intravenous route is used only if intramuscular administration is not feasible. The 500 mg. dose is added to the 200 ml. of sterile diluent and administered 60 to 80 drips/minute.

When used as intraperitoneal instillation, the above dose is diluted in 20 ml. of sterile diluent. If possible, instillation should be postponed until after patient is fully recovered from effects of anesthesia and muscle-relaxing drugs.

As aerosol treatment, 250 mg. of Kantrex is diluted with 3 ml. of physiological saline and nebulize.

Kantrex Injection in concentrations of 0.25 per cent (2.5 mg./ml.) has been used satisfactorily as an irrigating solution in abscess cavities, pleural spaces, peritoneal and ventricular cavities.

SUPPLIED:
Rubber capped vials as a ready-to-use sterile aqueous solution in two concentrations:

KANTREX INJECTION (kanamycin sulfate injection)
NDC 0015-3502-20—500 mg. per 2 ml.
NDC 0015-3502-24—Disposable Syringe (500 mg. per 2 ml.)
NDC 0015-3503-20—1.0 Gm. per 3 ml.
KANTREX PEDIATRIC INJECTION (kanamycin sulfate injection)
NDC 0015-3512-20—75 mg. per 2 ml.
(activity assayed as kanamycin base)

BRISTOL™ BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, New York 13201

New!

SURGICAL ENDOCRINOLOGY
Clinical Syndromes

●

Edited by
STANLEY R. FRIESEN, M.D., Ph.D.(Surg.)
with 28 contributors

Here is up-to-the-minute, useable information on the known endocrine syndromes requiring the attention of surgeons and other physicians. The book encompasses all the surgically significant endocrinopathies, both common and rare, all ages of patients, from the newborn to the elderly, and all accepted techniques of clinical and laboratory diagnosis, as well as surgical and conservative management.

The relevant basic sciences are integrated with current diagnostic and therapeutic techniques. Each of the contributors is a leading authority writing on his own area of special interest.

Among the unique features of this text you'll find an illuminating commentary on each chapter by Dr. Friesen . . . step-by-step diagnostic flowcharts . . . a central table of the humoral and biological actions of 20 important endocrine syndromes . . . mnemonic names for the syndromes . . . diagrammatic illustrations depicting the pathophysiology of each syndrome as a composite of clinical findings.

The volume presents a wealth of extraordinarily current developments, featuring information on such innovative concepts and practices as the APUD series of endocrine cells—their origin, identification, and clinical applications, and the future surgical management of endocrinopathies via transposition and transplantation of endocrine tissues.

430 Pages / 110 Illustrations / 1978 / $29.00

Lippincott

J. B. LIPPINCOTT COMPANY
East Washington Square ● Phila., Pa. 19105
In Canada: J. B. Lippincott Company of Canada Ltd.
75 Horner Avenue, Toronto, Ontario M8Z 4X7

Please send me:
Friesen: SURGICAL ENDOCRINOLOGY $29.00
Name ______________________
Address ______________________
City ______________ State ______ Zip ______
☐ Payment enclosed (Save postage and handling)
☐ Charge and bill me (Plus postage and handling)
Also available at your medical bookstore AS 7/79

Quick Reference To Surgical Emergencies

■

Edited by Gerald W. Shaftan, M.D.
and Bernard Gardner, M.D.

This handy manual, packed with clinical data in easy-to-use outline form, is designed for instant use in helping you evaluate the surgical emergency, make the diagnosis and carry out the indicated treatment.

Divided into two broad categories of traumatic and non-traumatic surgical emergencies the book systematically covers: Techniques of evaluating the patient and applying diagnostic criteria . . . Radiologic procedures that are necessary . . . Anesthesia considerations . . . Fluid and electrolyte replacement.

The patient evaluating techniques, diagnostic steps and surgical treatment are presented step-by-step with each individual entry numbered for simplicity.

Subject matter includes emergencies occurring in the areas of general, orthopaedic, neurologic, ophthalmic, thoracic, plastic, urologic, head and neck, and pediatric surgery.

All who are involved in surgical emergency treatment will appreciate this easy-to-use, time-saving manual.

664 Pages • 50 Illustrations • 1974
Flexible Binding • $23.75

Lippincott

J. B. Lippincott Company
East Washington Square • Phila., Pa. 19105

Please send me:

☐ QUICK REFERENCE TO SURGICAL EMERGENCIES $23.75

Name ____________________

Address ____________________

City ______________ State __________ Zip ____

☐ Payment enclosed (Save postage & handling) ☐ Charge and bill me (Plus postage & handling)

Also available at your medical bookstore. AS 7/79

Tablets

PERCOCET®-5 CII

Brief Summary of Prescribing Information

DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS

DEA Order Form Required.

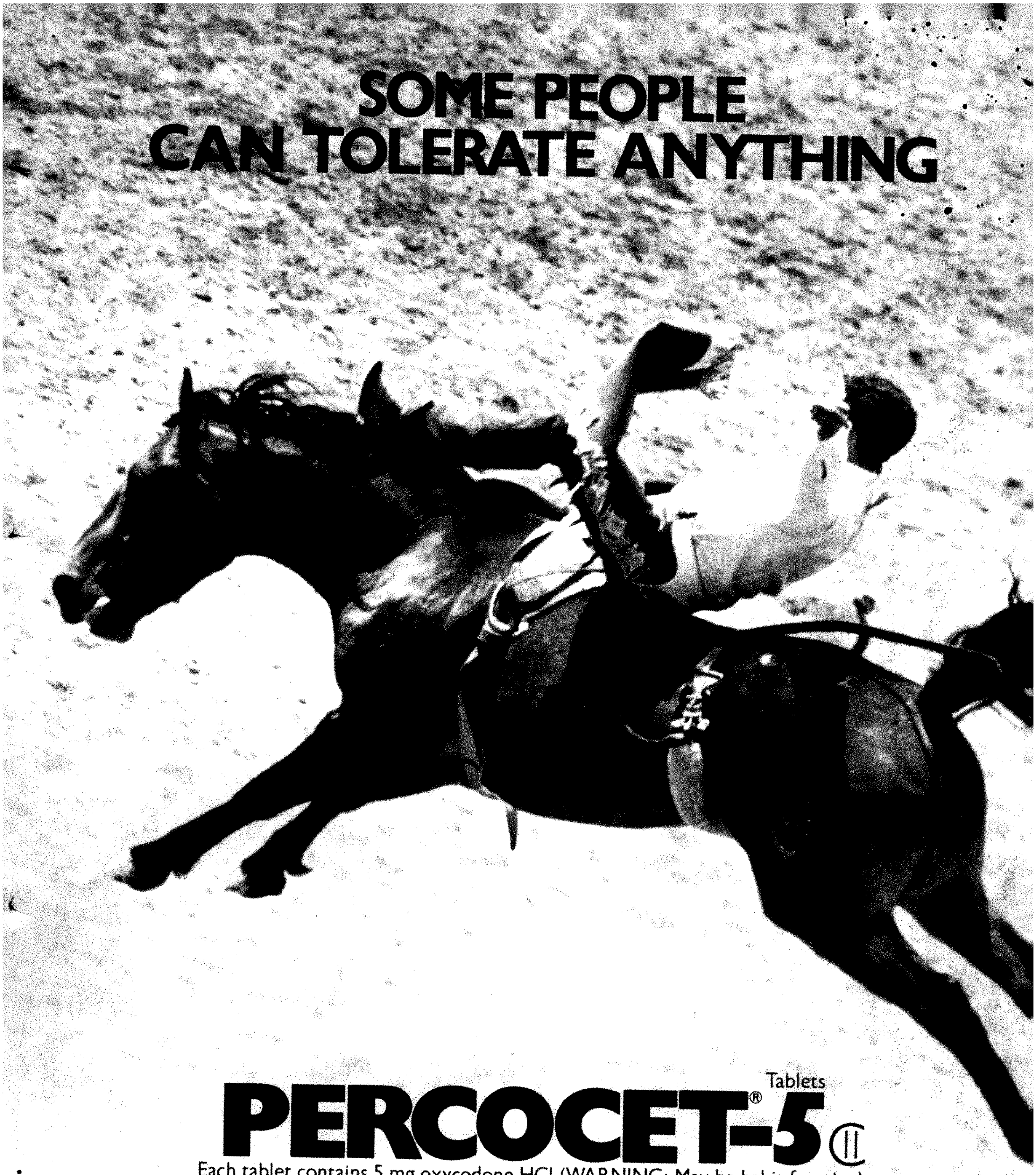
PERCOCET® is a U.S. registered trademark of Endo Inc.

Endo Inc.

Manati, Puerto Rico 00701
Subsidiary of Endo Laboratories, Inc
Subsidiary of the DuPont Company

DUPONT

EDO 644E 579



Tablets
PERCOCET®-5 CII

Each tablet contains 5 mg oxycodone HCl (WARNING: May be habit forming)
and 325 mg acetaminophen (APAP)

...FOR THOSE WHO CAN'T TOLERATE ASPIRIN

- ☐ indicated for moderate to moderately severe pain
- ☐ contains well-tolerated acetaminophen
- ☐ provides the effective analgesia of oxycodone
- ☐ scored tablet permits finer titration
- ☐ convenient, economical q6h dosage

Please see opposite page for brief summary of prescribing information.

"Current abstracts are amplified and illuminated by comments of the members of the Editorial Board, based on their own clinical experiences as well as those of other recognized authorities" . . . just one of the reasons why Lippincott's

Current Surgery

Formerly REVIEW OF SURGERY

Editor: Lloyd M. Nyhus, M.D.
Associate Editors: Robert E. Condon, M.D.,
W. G. Schenk, Jr., M.D., Seymour Schwartz, M.D.

helps Resident (special rate only **$16.00**) and Veteran Surgeon alike to keep up with current progress, trends, and attitudes in all branches of surgery and the surgical specialties.

A true saver of precious reading time—from its detailed Contents Pages to its meaty reviews, and abstracts especially classified for reader convenience—a typical issue includes:

- Focus—several Reviews of timely or other special significance
- An original Report of major importance
- Twenty or more Abstracts with Commentary (and oft-times, rebuttal)
- Residents Corner—comprising Brief (1 to 3-page) Reports and Investigations
- In-depth Reviews of Current Books in Surgery

TO PUT THE BIMONTHLY CURRENT SURGERY AT YOUR FINGERTIPS NOW,

SUBSCRIBE TODAY . . .

J. B. LIPPINCOTT COMPANY, East Washington Square, Philadelphia, Pa. 19105 AS 7/79

Please enter my subscription to CURRENT SURGERY for 1 year (6 issues), at ☐ **$20** (U.S.); ☐ **$24** (all other countries); Resident Rate ☐ **$16** (U.S. only; also note "year" of residency and Specialty ____________________).

PLEASE PRINT
Name ____________________
Address ____________________
City/State/Zip ____________________

☐ Payment Enclosed.
☐ Charge my account.
My Specialty is:
____

Hemostasis in Massively Transfused Trauma Patients

R. B. COUNTS, C. HAISCH, T. L. SIMON, N. G. MAXWELL, D. M. HEIMBACH, C. J. CARRICO

Twenty-seven patients requiring massive transfusions were studied prospectively to determine whether administration of stored, modified whole blood induced a primary disorder of hemostasis evidenced by generalized microvascular oozing. Platelet counts fell in proportion to the number of units of blood transfused. In contrast, the levels of factors V and VIII correlated poorly with the units of blood transfused, 85% of the total variation in the levels being due to influences other than transfused blood. Levels of all other clotting factors were unrelated to the number of units of blood given. Eight patients developed abnormal bleeding. The cause appeared to be dilutional thrombocytopenia in five patients, and DIC in three. In six of the eight, bleeding was controlled with platelet concentrates alone. Two patients were given cryoprecipitate also. The most useful laboratory test for predicting abnormal bleeding was the platelet count. Fibrinogen levels should be followed as an aid in the diagnosis of DIC. The BT, PT, and PTT were not helpful in assessing the cause of bleeding, unless they were greater than 1.5 times the control value. We recommend that any patient receiving massive transfusions who develops diffuse microvascular bleeding be given platelet concentrates. Platelet counts as high as 100,000 may be required to control bleeding from surgical woulds. It is not necessary to supplement transfusions of stored, modified whole blood with fresh blood or fresh frozen plasma.

From the Puget Sound Blood Center, and the Departments of Medicine and Surgery, University of Washington, Seattle, Washington

A MAJOR CHANGE IN COMMUNITY blood banking practice in the last ten years has been the widespread adoption of blood fractionation and specific component transfusion which allows the provision of platelets, cryoprecipitate and albumin for patients with special needs for these components.

In many communities, red cells are used almost exclusively for transfusion. These are supplemented with albumin or other volume expanders and with plasma if necessary. The use of red cells and albumin for transfusion to patients who are bleeding is inefficient since approximately 450 ml of plasma must be processed to yield one 250 ml bottle of 5% albumin. A more efficient fractionation scheme consists of the salvage of both platelet concentrates and cryoprecipitate from a unit of whole blood using a triple-bag system. The supernatant plasma after cryoprecipitate removal is returned to the red cells to provide "modified whole blood" which differs from whole blood in having had 85% of the platelets, 60% of the factor VIII and about 25% of the fibrinogen removed.[19] The Puget Sound Blood Program provides modified whole blood for bleeding patients, who need, simultaneously, both red cells and plasma volume replacement.

Concerns about depletion of platelets and coagulation factors in patients who receive large volumes of blood within a short time have led to recommendations that transfusion of stored or modified whole blood be supplemented with "fresh warm blood" from walking donors.[8,15] Others have suggested that fresh blood or fresh frozen plasma is necessary, when large volumes of stored blood are transfused, in order to provide coagulation factors.[1,22] We have examined the hypothesis that transfusion of modified whole blood leads to a primary defect in hemostasis because of depletion of platelets of clotting factors. Our results demonstrate that transfusion of large volumes of modified whole blood does lead to dilutional thrombocytopenia but does not cause clinically significant coagulation factor deficiencies. These findings have important implications for both the clinical management of massively bleeding patients and the management of community blood resources in this country.

Procedures

Patients

The study group consisted of 27 patients who sustained major trauma, massive GI hemorrhage, or aortic aneurysm rupture and who were admitted to the Trauma Center at Harborview Medical Center with systolic blood pressure less than 80 mmHg. The patients ranged in age from 18 to 80. Whole blood was drawn from healthy random donors at the Puget Sound Blood Center

---

Reprint requests: Dr. R. B. Counts, Puget Sound Blood Center, Terry and Madison Streets, Seattle, Washington 98104.

Supported by NIH Grants HL-17265 and NIGMS-24990.

0003-4932/79/0700/0091 $00.95 © J. B. Lippincott Company

into CPD anticoagulant and stored at 2–6° according to standard procedures.

Platelet concentrates were produced according to the method of Slichter and Harker.[20]

Cryoprecipitated AHF was prepared by the method reported by Slichter et al.[19] using a refrigerated freezing-thawing bath (Forma Scientific, Marietta, Ohio) that allows the cryoprecipitate to be removed and modified whole blood to be available for transfusion within eight hours of the time the blood was collected.

Platelet counts were performed in duplicate using an electronic particle counter.[2]

Blood for coagulation screening tests and clotting factor assays was collected by venipuncture into plastic tubes. It was anticoagulated with 1/10 volume of 3.8% sodium citrate with appropriate adjustment for hematocrit if the patient was anemic. Samples were spun at 4500 × *g* for 30 minutes to remove platelets. The platelet-poor plasma was frozen at −70° until assays were performed.

Tests of coagulation were done by standard methods: the prothrombin time (PT) by the method of Quick using human brain thromboplastin,[13] the partial thromboplastin time (PTT) by the method of Proctor and Rapaport.[12] Fibrinogen was measured as total clottable protein.

Factors V, VII, X and prothrombin were assayed by a one-stage test based on the prothrombin time using human brain thromboplastin. Factors VIII, IX, and XI were determined by one-stage PTT-type assays[7] using human brain cephalin. Normal plasma for coagulation standards was a pool of plasmas from 30 healthy random donors. Plasmas deficient in factor VIII or factor IX were obtained by plasmapheresis of patients with severe hemophilia A or B. Plasma deficient in factor V was aged, oxalated plasma. Plasmas deficient in factors II, VII, X, or XI were purchased from George King Biomedical, Salem, New Hampshire. Bleeding times (BT) were determined by the Ivy template method.[6]

Assays of Clotting Factors in Stored Blood

Ten units each of whole blood, modified whole blood (platelets removed) and modified whole blood (cryoprecipitate removed) and eight units of modified whole blood, (both platelets and cryoprecipitate removed) were stored in a blood bank refrigerator at 2–6°. Samples for assays were removed by an aseptic technique, at the time the blood was collected (zero time), and at one to five day intervals over a period of 21 days. Duplicate assays were performed on each sample for clotting factors II, V, VII, VIII, IX, X, XI and fibrinogen.

Patient Studies

All patients were initially resuscitated by emergency paramedics ("Medic One", Seattle Fire Department) using only Ringer's Lactate solutions for blood volume expansion. Initial blood samples were obtained at Harborview Medical Center immediately upon entering a patient in the study. Subsequently, samples were obtained at approximately 12 hour intervals for 96 hours, or more frequently if the patient was felt clinically to have abnormal bleeding. Bleeding caused by a primary disorder of hemostasis was distinguished from "surgical bleeding" by two criteria. 1) It involved diffuse microvascular oozing rather than rapid bleeding from an identifiable lesion. 2) It was manifested by bleeding from multiple areas such as wound skin margins and venipuncture sites in addition to the operative site itself.

We attempted in each case to obtain the initial blood sample before the patient received any blood components. Transfusion of blood components was guided by the clinical judgement of the attending surgeons. Platelet concentrates, plasma or cryoprecipitate were given only when there was abnormal, microvascular bleeding and laboratory evidence of a platelet or coagulation factor deficiency. Screening tests (thrombin time, prothrombin time and PTT), platelet counts, and specific assays for each of the clotting factors were performed on all samples drawn for this study.

Analysis of Data

Standard statistical methods were used for data analysis. Regression lines were calculated by the least-squares method and correlations estimated by calculation of the coefficient of determination r^2.[4] Analysis of variance was used to calculate variance ratios, distributed as F, to test the significance of regression.[3]

Results

Clotting Factors in Stored Blood

The only clotting factors which deteriorated significantly on storage were factors V and VIII (Fig. 1). There was no difference between the rate of disappearance of factor V activity from modified whole blood and the rate of disappearance from whole blood from which either cryoprecipitate or platelets or both had been removed, *i.e.*, the regression lines for whole blood, cryoprecipitate-poor blood, platelet-poor blood, and cryoprecipitate-poor-platelet-poor blood were identical. The disappearance of factor V appeared, surprisingly, to be linear with time, zero-order in factor V concentration. Factor V levels remained above 50% of normal for at least 14 days of storage at 4°. The mean factor V level at 21 days was 35 ± 7% (1 S.D.) of the starting level.

The mean level of residual factor VIII activity in modified whole blood following cryoprecipitate removal was 15%. Figure 1 shows the disappearance of factor VIII in platelet-poor modified whole blood. The initial decay of factor VIII activity had a $t_{1/2}$ of about 24 hours for the first two days. By 48 hours the activity had decreased to 30% of the initial activity, approximately the minimum level necessary for hemostasis. The mean levels of other factors in whole blood and modified whole blood after 21 days of storage are given in Table 1. Except for factors VIII and V, all factor levels were higher than 57% of the original blood level after 21 days of storage.

Clinical Studies

During the study, 893 units of blood were administered to the 27 patients, a mean of 33 units per patient, the range was from 8–65 units. Of this total, 621 units (69%) were administered within the first 24 hours of hospitalization, 114 units (13%) between days one to five and 158 units (18%) later.

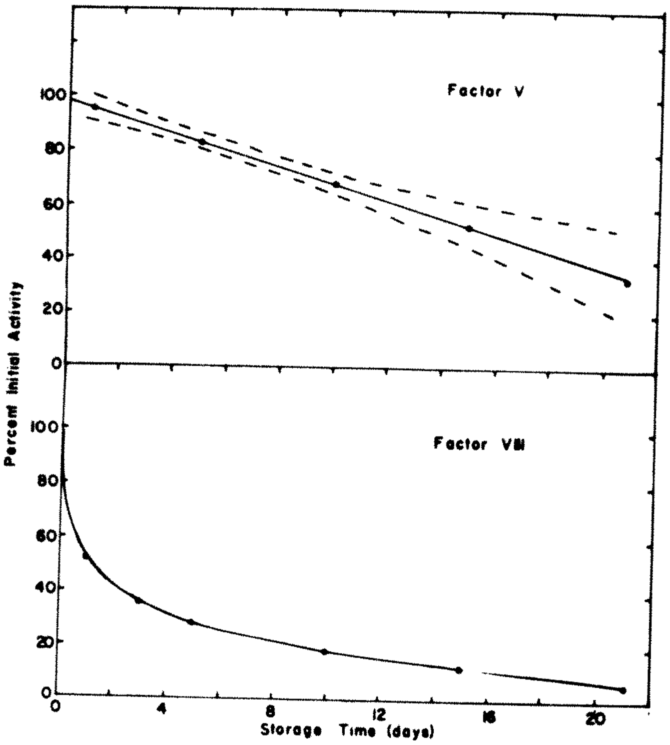


FIG. 1. Levels of factors V (above) and VIII (below) in CPD-anticoagulated blood stored at 4°. Least squares regression lines for factor V calculated from assays of ten units of blood from normal, random donors. The 95% confidence limits are given for factor V. For factor VIII the initial half-time is 24 hours.

TABLE 1. *Clotting Factor Levels in Modified Whole Blood (CPD Anticoagulant) Stored at 4°*

Clotting Factor	Level After Storage (Days) as a Percentage of the Initial Level: 14 Days	21 Days
Prothrombin	87	70
VII	57	66
IX	106	97
X	90	85
XI	99	107
XII	133	117
Fibrinogen	98	109

Only nine units (1%) of blood were administered within 24 hours of the time they were collected. Four hundred seventy-nine units (59%) were one to five days old at the time of transfusion; 202 units (23%) were six to ten days old and 191 units (21%) were 11–21 days old. Thus, about half the blood was less than five days old when it was transfused, and 75% was less than 10 days old.

The kinds of blood components transfused are listed in Table 2. Only 5 of 893 units were unprocessed whole blood. Eighty-three per cent of the blood transfused was modified whole blood which had either platelets or cryoprecipitate, or both, removed. Almost half the units transfused (419 units—47%) had had cryoprecipitate removed.

Platelets

To analyze the effect of transfusion of blood on the platelet count, platelet counts were plotted against the number of units of blood which the patient had received up to the time the sample was obtained for the platelet count (Fig. 2). Each point on the graph represents a platelet count obtained prior to the transfusion of any platelets. There was a strong relationship

TABLE 2. *Types of 893 Units of Blood Distributed by Blood Center and Administered to 27 Patients*

	Number	
1. Cryo-poor whole blood	170	19
2. Platelet-poor whole blood	326	36
3. Cryo and platelet-poor whole blood	249	28
4. Whole blood	5	1
5. Red blood cells	122	14
6. Unidentified	21	2
Total	893	100

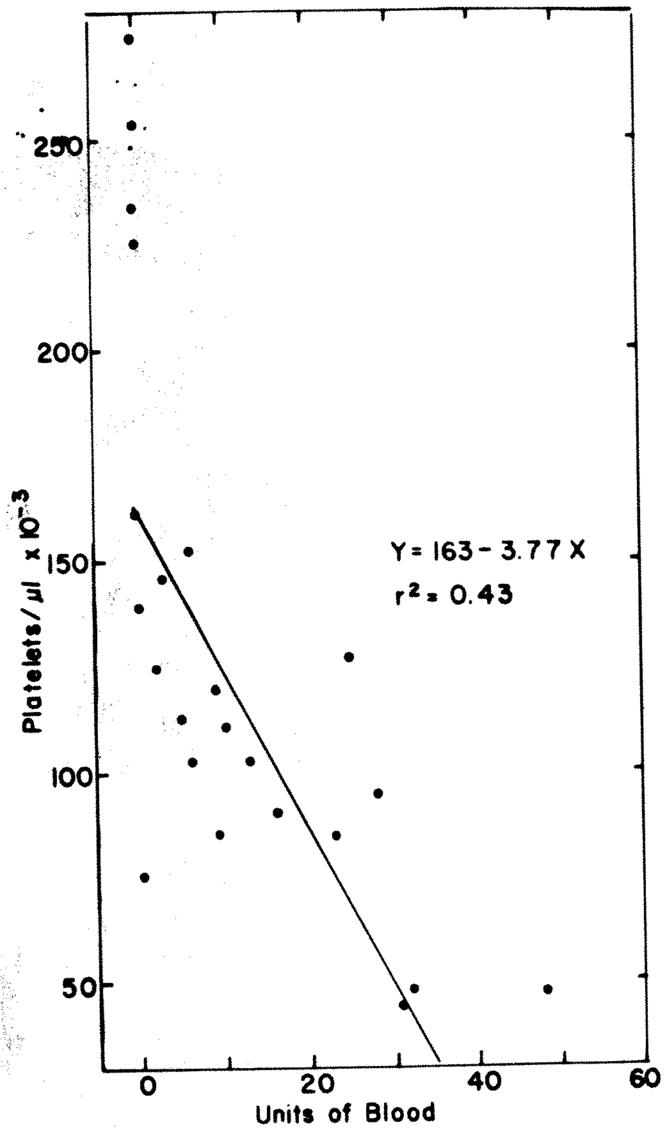


FIG. 2. Plot of platelet counts against the number of units of blood transfused to the patient prior to the time the sample was obtained for the platelet counts. No platelet transfusions had been given to any of the patients represented in this graph.

between thrombocytopenia and the number of units of blood transfused up to the time the platelet count was done. The regression was highly significant (F = 25.7; 1, 34 D.F.; $p = 1 \times 10^{-5}$). There was considerable variation in the platelet levels, however, the coefficient of determination, r^2, was 0.43.

Factors V and VIII

The levels of factors V and VIII tended to be lower in patients who had received a large amount of blood than in patients who had received no blood (Figs. 3 and 4). In each case, the slope of the least squares regression line was significantly different from zero as estimated by the analysis of variance; but the coefficient of determination for each line was less than 0.2.

Factor VII

Figure 5 is a scatter diagram of factor VII levels against the number of units transfused up to the time the sample was drawn. The correlation is poor ($r^2 = 0.09$), the regression is not statistically significant (P = 0.07). The total variance in factor VII levels was large. It was not possible to predict the level in a given patient from the units of blood he had received.

Fibrinogen

Fibrinogen level as a function of units of blood received by the patient is plotted in Figure 6. There is no correlation between the two variables. The results of similar analysis of factors X, XI, and XII were similar to fibrinogen. The levels of each of these factors appeared to be completely unrelated to the number of units of blood transfused.

Clinical Course of Patients

Nineteen of the 27 patients studied had no abnormal bleeding. Eight had a primary hemostasis abnormality within 48 hours of admission, manifested by uncontrolled oozing at multiple sites (such as skin margins and venipuncture sites) in addition to the surgical

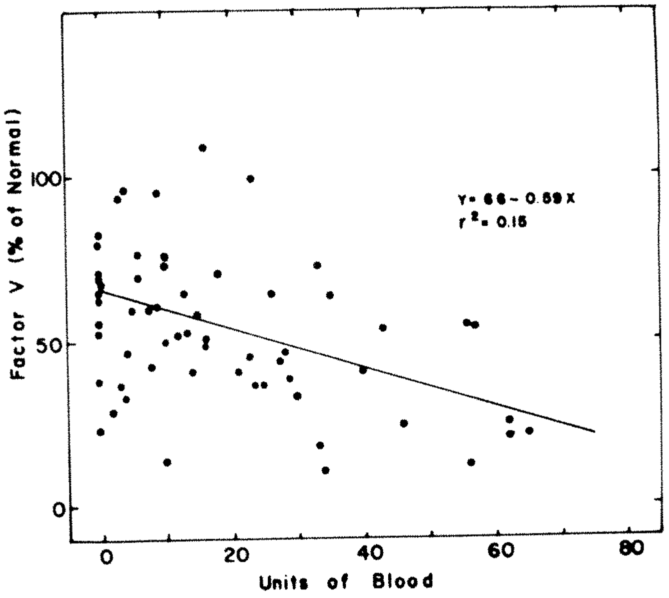


FIG. 3. Factor V levels in patients plotted against the number of units of blood transfused prior to the time the sample was obtained for assay. The regression was statistically significant: F = 14.92; 1,58 d.f.; p = 0.001.

wound. Data obtained when these patients had abnormal bleeding are presented in Table 3. In five patients, the coagulation factors were in the normal range. Three patients had consumption of platelets and fibrinogen as well as low levels of factors V and VIII, suggesting intravascular coagulation (DIC).

The mean number of units of blood received by the patients who bled, prior to the onset of medical bleeding was 35. There was no difference in the means of lowest platelet counts recorded for the patients who had abnormal bleeding and those who did not. Likewise, the differences between the means of the lowest levels of fibrinogen and factors V, VII, IX, and X for the two patient groups were not statistically significant. Factor VIII levels were significantly lower in the group of patients who had abnormal bleeding compared with those who did not. However, the lowest levels of factor VIII measured were greater than 30% of normal in all of the patients with medical bleeding except for two who had DIC (documented by low platelets and

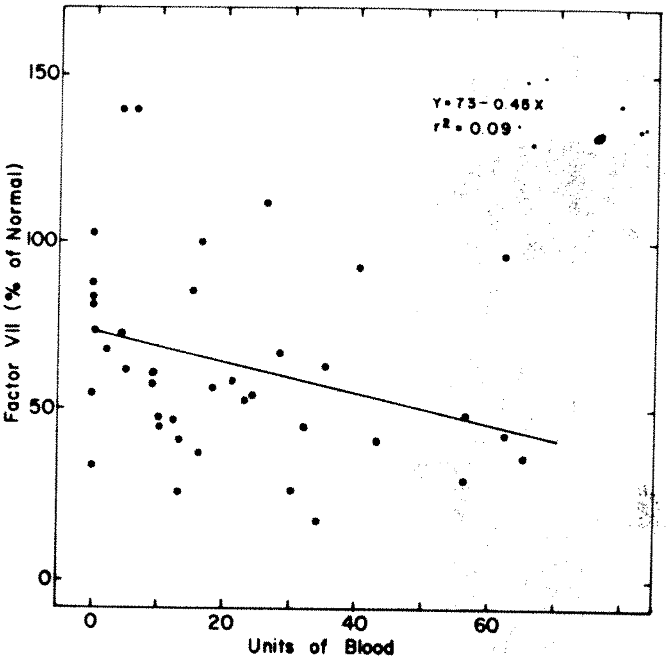


FIG. 5. Scatter diagram of factor VII plotted against units of blood transfused. The statistics for the regression are: F = 3.57; 1, 38 d.f.; p = 0.07.

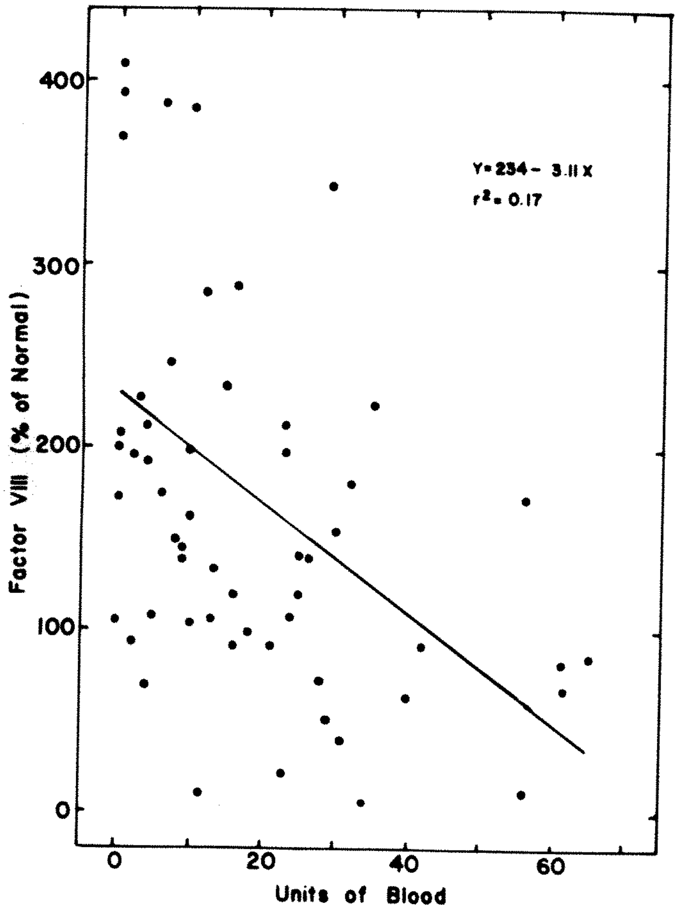


FIG. 4. Factor VIII levels in patients plotted against the number of units transfused prior to obtaining the sample. The regression was statistically significant: F = 11.68; 1,56 d.f., p = 0.001.

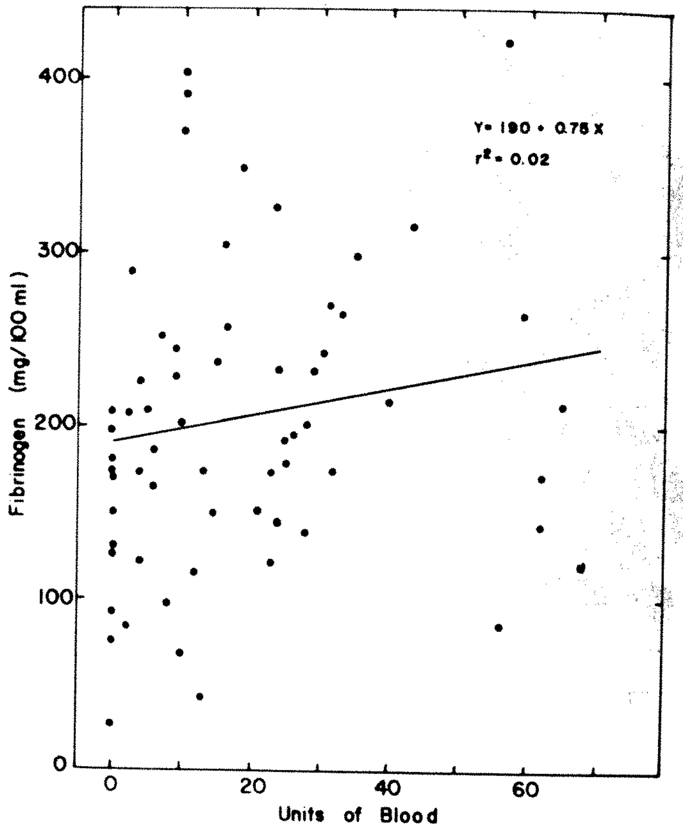


FIG. 6. Scatter diagram of fibrinogen plotted against units of blood transfused. The statistics of the regression are: F = 1.00; 1,60 d.f.; p = 0.32.

TABLE 3. *Hemostasis Tests and Treatment of Patients Having Generalized Bleeding*

		Levels at Time of Bleeding					Blood Components in First 48 hr of Admission		
Pt. No.	Clinical Problem	Platelet Count	Fibrinogen	BT	VIII	V	Mod. W.B.	Platelets	Cryoprecipitate
10	Aortic aneurysm	140,000	198	20′	124	71	16	10	0
16	Aortic aneurysm	90,000	225	18′	192	96	35	14	0
18	Stab wound abdomen	60,000	117	30′	—	52	62	40	0
19	Soft tissue trauma. Retroperitoneal hematoma	50,000	173	23′	40	18	59	12	10
20	Severe chest trauma	70,000	307	21′	93	54	56	28	0
21	Post antrectomy for duodenal ulcer	32,000	28	30′	6	11	62	20	0
22	Aortic aneurysm	85,000	144	13′	108	37	30	12	6
23	Soft tissue trauma, skull fracture	81,000	68	17′	21	14	27	12	0

fibrinogen and evidence of ongoing consumption). There was good correlation between the levels of factors V and VIII and between factor VIII and fibrinogen in samples obtained from the patients who had medical bleeding, including the three who had abnormally low factor V and VIII levels.

Of the eight patients who had abnormal bleeding, six were treated only with modified whole blood and platelet concentrates. In each of these cases, bleeding was controlled shortly after platelet transfusions were given. The other two patients also received plasma or cryoprecipitate in addition to modified whole blood and platelets. In all patients, generalized bleeding was controlled within 12 hours of its onset. No patient in the study died as a direct consequence of bleeding or had uncontrolled bleeding at the time of death.

Screening Tests

The bleeding times, prothrombin times and partial thromboplastin times done at the time of bleeding in patients who had abnormal bleeding were compared with those performed on samples from patients without abnormal bleeding in order to assess the value of these screening tests for predicting whether a patient will develop abnormal bleeding. The ratio of the patient's clotting time to the normal plasma control clotting time was used to normalize the results.

Thirty-seven samples were obtained within 24 hours of admission from the 19 patients without abnormal bleeding. The mean of the prothrombin times in this group was 1.23 ± 0.14 (1 S.D.) times the control. The mean PTT was 1.12 ± 0.23 times control. For the eight patients who developed generalized bleeding, the mean PT at the time of bleeding was 1.63 ± 0.50 times the control and the mean PTT 1.68 ± 0.69 times the control. Although the means for the patients with generalized bleeding were considerably higher than those for non-bleeding patients, the variability was also greater. Indeed, the predictive value of the PT and PTT was poor when the results were analyzed according to whether patients with moderately abnormal PT and PTT had generalized bleeding or not (Table 4). For purposes of analysis, a level of 1.3 times the control was selected as moderate prolongation. This corresponds in our system to a PT of 19 seconds and a PTT of 53 seconds. Of samples in which the PT $\geq$ 1.3 times the control, seven were from patients with abnormal bleeding, eight were from patients without abnormal bleeding. Of nine samples with the PTT $\geq$ 1.3 times the control, five were from patients with abnormal bleeding, four were from patients without abnormal bleeding.

The PT and PTT were fair predictors of bleeding only when they were markedly prolonged. Of six samples where the PT and PTT were $\geq$1.5 times control (PT

TABLE 4. *Number of Patients Having Prolonged PT or PTT*

	Prothrombin Time				PTT			
Patient Category	<1.3 × Control	>1.3 × Control	>1.5 × Control	Total No. Pts.	<1.3 × Control	>1.3 × Control	>1.5 × Control	Total No. Pts.
Generalized bleeding	1	7	4	8	3	5	4	8
No generalized bleeding	11	8	2	19	15	4	2	19
Total	12	15	6	27	18	9	6	27

For patients with bleeding, the results of tests at time of bleeding are tabulated; for non-bleeding patients, the longest PT and PTT.

22 seconds, PTT 62 seconds) four were from patients with abnormal bleeding, two from patients without abnormal bleeding.

In a similar way, the template bleeding times did not discriminate well between bleeding and nonbleeding patients because of large overlap. Although all patients with generalized bleeding had a BT ≥ 10 min and seven (88%) had a BT ≥ 15 minutes, 12 (63%) of patients without generalized bleeding had a BT ≥ 10 and nine (47%) had a BT ≥ 15 minutes at some time within the first two days of hospitalization. Thus, of 20 patients with a BT ≥ 15 minutes, 56% did not have generalized bleeding.

Discussion

By individualized component therapy and extensive component fractionation, it is possible for community blood banks to provide components needed by several patients from each unit of blood donated. Using a triple-bag system, for example, platelet concentrates, cryoprecipitated AHF and modified whole blood, lacking these fractions, can be produced. The applicability of this system depends upon the safety and efficacy of modified whole blood for transfusion in patients who have simultaneous volume and oxygen transport deficiencies requiring transfusions of whole blood.

We have sought to determine the composition of modified whole blood in regard to hemostatic components, to compare it with unfractionated whole blood, and to attempt to determine if an association exists between platelet and clotting factor levels in patients and the number of transfusions they received.

Platelets

There are several possible causes of thrombocytopenia in trauma patients. The most important are dilution by transfused blood or other fluids, and consumption of platelets. Platelets, in blood which is refrigerated, rapidly become nonviable.[11] Furthermore, adults, at least, have a limited ability to increase their platelet production acutely and have little or no readily mobilizable platelet pool.[16]

That transfusion of large volumes of blood should cause thrombocytopenia is therefore, relatively predictable. It has been suggested that as little as ten units of blood transfused into an adult may cause clinically significant thrombocytopenia. However, our results (Fig. 2) suggest that, on the average, the platelet count would fall below 100,000 after transfusion of 18 units of blood. Studies in normals have shown the bleeding time to be normal if the platelet count is 100,000/μl or greater unless there is platelet dysfunction.[6] This, it seems reasonable to anticipate that thrombocytopenia may become a clinically significant problem after an adult has received 15–20 units of blood (about 1.5–2.0 times his blood volume). Only two patients in our study had platelet counts less than 100,000 after having received less than 18 units of blood. One of these had a platelet count of 76,000 before any blood was transfused. This patient had a ruptured abdominal aortic aneurysm; it is probable that local consumption of platelets at the site of the aneurysm was responsible for the thrombocytopenia.

Slightly less than half the variation in platelet counts in this study could be ascribed to the functional relationship between blood transfused and the platelet count. A number of factors occurring in trauma patients cause platelet consumption. These include massive brain, lung or other soft tissue damage, severe shock, hypoxia, sepsis and endothelial damage.[14,17]

The most useful parameter for estimating the need for platelet transfusions in our patients was the platelet count. In contrast, the bleeding time proved to be of little help in predicting whether a trauma patient would have abnormal bleeding because the bleeding time was commonly prolonged in patients who did not develop microvascular bleeding as well as those who did. This agrees with the findings of Miller, et al.[10] who noted that the Ivy bleeding time was prolonged in all of their patients by the time they had received five units of blood and well before any patient developed abnormal bleeding. Thus, the bleeding time, in addition to being difficult to obtain under emergency operating room conditions, does not appear to be helpful in anticipating the onset of microvascular bleeding.

Coagulation Factors

The only clotting factors which are labile on storage at 4° are factors V and VIII. Fibrinogen and the vitamin K-dependent proenzymes are preserved in blood stored for 21 days at levels greater than 60% of their activities in fresh blood or fresh frozen plasma (Table 1). Thus, plasma transfusion is not needed to supplement modified or stored whole blood transfusions in patients with liver failure, vitamin K deficiency or warfarin anticoagulation who are bleeding.

Factor V is generally considered to be quite labile on storage at 4° in ACD blood.[21] Our data suggest that factor V, at least under present-day storage conditions, is not as labile as has been thought, the mean level remaining above 50% for more than two weeks. The clinical measurements also show that a patient's factor V level cannot be predicted from the number of units of modified whole blood he has received. Other variables which affect a patient's factor V level include the rather large variation between normal individuals,[9] severe hepatic failure[5] and consumption.[17]

Factor VIII is the most unstable of the clotting proteins (Fig. 1), the level of CPD blood falling below 50% in less than 24 hours of storage at 4°. Like platelets, factor VIII cannot be effectively replaced by the transfusion of whole blood. However, our studies of factor VIII levels in trauma patients (Fig. 4) indicate that the level of factor VIII is rarely below 50%. Furthermore, although the slope calculated for the regression line in Figure 4 is, statistically, significantly different from zero, the low coefficient of determination (0.15) indicates that 85% of the total variability in the patients' factor VIII levels is attributable to causes other than dilution by the blood transfused.

Our data confirms other studies showing a large physiological reserve of factor VIII and higher than normal levels in patients after trauma or operations. As in the case of factor V, individual patients may have low levels, but the level cannot be predicated from the amount of blood transfused. Rather, the concordance between levels of factors VIII and V and fibrinogen suggests that consumption of these proteins is the major cause of the occasional deficiencies in our patients.

Other Clotting Factors

The results of assays of factor VIII and fibrinogen are representative of other clotting factor levels in the trauma patients. In each case, there was essentially no functional relationship between the amount of blood transfused and the measured activity of the protein.

This study demonstrates that transfusion of modified whole blood of random age to trauma patients needing large volumes of blood does not cause clinically significant clotting factor deficiencies. Thus, to supplement transfusions of modified whole blood with fresh blood or fresh frozen plasma, in order to provide clotting factors is unnecessary and wasteful. Platelet transfusions are frequently necessary after a patient receives blood transfusions in excess of about 1.5 times his normal blood volume.

These results have important implications for the management of blood resources. They suggest that the emphasis which many have placed on increasing the fraction of transfusions given as packed red cells is inappropriate. It has been recommended that up to 85% of transfusions should be given as red cells, and that albumin or frozen plasma be given if additional volume is needed. In our region, 37% of the blood transfused is given to patients who receive five or more units of blood, patients who require volume expansion as well as oxygen transport capacity. An unrealistically high use of red blood cells tends to increase the demand for albumin and plasma.

Eight of the 27 patients in our study developed generalized oozing, usually at the time of operation. In six of these (Table 3), the bleeding was controlled with platelet transfusions. In five of the six, the platelet count at the time of bleeding was <100,000/μl and clotting factors were adequate for hemostasis. The sixth had a platelet count of 140,000 but bleeding was rapidly controlled after administration of six units of platelets.

The most useful readily available laboratory tests for predicting abnormal bleeding and guiding therapy proved to be the platelet count and fibrinogen level. The PT, PTT, and BT correlated well with generalized bleeding when they were markedly prolonged, but many patients who did not develop generalized bleeding had moderate abnormalities of these tests.

We recommend that patients who need both red cells and volume replacement be treated with whole blood or modified whole blood rather than with red cells and albumin or plasma. When a patient receives more than 15 units of blood, the platelet count should be followed and the surgeon should be alert to signs of generalized oozing. Platelet concentrates are usually indicated if a patient receives over 20 units of blood in a 12 hour period. If abnormal bleeding occurs, platelet concentrates should be given and the platelet count coagulation tests obtained in order to make a specific diagnosis, the most likely disorders to be considered being dilutional thrombocytopenia and DIC. Valuable time for selection of proper therapy may be lost by the presumption that clotting factors have been diluted by transfused blood.

Acknowledgments

The authors thank Lela Lancaster Bennett, Ruth Henerson and Michael Joseph for performing the coagulation assays, Dr. Michael Copass, the Seattle Fire Department's "Medic One" paramedics and the staff of the Harborview Medical Center Trauma Unit for valuable assistance in the patient studies and Dr. Dennis Donohue for helpful discussions.

References

1. American Association of Blood Banks Technical Manual. 7th Ed., Washington, D. C. 1977, p. 240.
2. Bull, B. S., Schneiderman, M. and Brecher, G.: Platelet Counts with the Coulter Counter. Am. J. Clin. Pathol., 44:678, 1965.
3. Draper, N. and Smith, H.: Applied Regression Analysis. New York, Academic Press. 1975.
4. Freund, J. D.: Mathematical Statistics. 2nd Edition. Englewood Cliffs, Prentice Hall. 1971.
5. Hallen, A. and Nilsson, I. M.: Coagulation Studies in Liver Disease. Thromb. Diath. Haemorr., 11:51, 1964.
6. Harker, L. A. and Slichter, S. J.: The Bleeding Time as a

Screening Test for Evaluation of Platelet Function. N. Engl. J. Med., 287:155, 1972.

7. Langdell, R. D., Wagner, R. H. and Brinkhous, K. M.: Effect of Antihemophilic Factor on One-Stage Clotting Tests. J. Lab. Clin. Med., 41:637, 1953.
8. Lim, Robert, C., Jr., Olcott, C., Robinson, A. J. and Blaisdell, F. W.: Platelet Response and Coagulation Changes Following Massive Blood Replacement. J. Trauma, 13:577, 1973.
9. Meade, T. W. and North, W. R. S.: Population Based Distributions of Haemostatic Variables. Br. Med. Bull., 33:283, 1977.
10. Miller, Ronald D., Robbins, T. O., Tong, M. J. and Barton, S. L.: Coagulation Defects Associated with Massive Blood Transfusions. Ann. Surg., 174:794, 1971.
11. Murphy, S. and Gardner, F. H.: Platelet Preservation: Effect of Storage Temperature on Maintenance of Platelet Viability-Deleterious Effect of Refrigerated Storage. N. Engl. J. Med., 280:1094, 1969.
12. Proctor, R. R. and Rapaport, S. I.: The Partial Thromboplastin Time with Kaolin. Am. J. Clin. Pathol., 36:212, 1961.
13. Quick, A. J.: Hemorrhagic Diseases and Thrombosis. Second edition. Philadelphia, Lea and Febiger. 1966.
14. Rapaport, S. I.: Defibrination syndromes. *In* Williams, W. J., Beutler, E., Ersler, A. J. and Rundles, R. W. (eds.) Hematology. Second edition. New York, McGraw-Hill. 1977, p. 1454.
15. Sheldon, G. F., Lim, R. C., Jr. and Blaisdell, F. W.: The Use of Fresh Blood in the Treatment of Critically Injured Patients. J. Trauma, 15:670, 1975.
16. Shulman, N. R., Watkins, S. P., Itscoits, S. B. and Students, A. B.: Evidence that the Spleen Retains the Youngest and Hemostatically Most Effective Platelets. Trans. Assoc. Am. Physicians, 81:302, 1968.
17. Silver, D.: Coagulapathies and Surgeons. J. Surg. Res., 16:429, 1974.
18. Simmons, R. L., Collins, J. A., Heisterkamp, C. A., et al.: Coagulation Disorders in Combat Casualties. Ann. Surg., 169: 455, 1969.
19. Slichter, S. J., Counts, R. B., Henderson, R. and Harker, L. A.: Preparation of Cryoprecipitated Factor VIII Concentrates. Transfusion, 16:616, 1976.
20. Slichter, S. J. and Harker, L. A.: Preparation and Storage of Platelet Concentrates. I. Factors Influencing the Harvest of Viable Platelets from Whole Blood. Br. J. Haematol., 34: 395, 1976.
21. Urbaniak, S. J. and Cash, J. D.: Blood Replacement Therapy. Br. Med. Bull., 33:273, 1977.
22. Wilson, R. F., Mammen, E. and Walt, A. J.: Eight Years' Experience with Massive Blood Transfusions. J. Trauma, 11: 275, 1971.

Erratum

In the article "Critical Evaluation of Hypertonic and Hypotonic Solutions to Resuscitate Severely Burned Children: A Prospective Study" by Fred T. Caldwell, M.D. and Bonny H. Bowser, B.S. (Ann. Surg., 189:546, 1979) the formula appeared incorrectly.

The formula *should* read: ml/kg·% and *not* ml/kg/dl.

Preoperative Assessment of Resectability for Carcinoma of the Thoracic Esophagus

Part I. Esophagogram and Azygogram

SHOZO MORI, M.D., MORIO KASAI, M.D., TOSHIO WATANABE, M.D., ISSEI SHIBUYA, M.D.

From the Second Department of Surgery,
Tohoku University Hospital,
Sendai, Japan

The length and radiologic type of tumor, esophageal axis and azygogram were examined in 208 patients with carcinoma of the thoracic esophagus who underwent esophageal resection from 1965 to 1975. An histologic examination was performed on all resected specimens. These examinations were used as diagnostic aids to determine the resectability of esophageal carcinoma before surgery. Tumor length did not seem an adequate parameter on deciding resectability; nor did the radiologic type of tumor. Examination of the esophageal axis was in determining resectability. The azygogram gave the most accurate information about resectability of these 4 parameters. The probability of a correct diagnosis regarding differentiation of noncurative a_3 lesions from other resectable lesions was 85.6%.

NINE HUNDRED SEVENTEEN CASES of esophageal carcinoma were treated at the Tohoku University Hospital, Sendai Japan from 1951 to 1975. Resection of the cancerous esophagus was performed in 704 patients and the resectability rate was 76.8%. In patients with stage I lesions namely n_0 and a_0* the one year survival was 77.3%, three year survival 61.1% and five year survival 46.7%. One year survival in patients with stage IV lesions, expecially of a_3 in which carcinoma infiltrated into adjacent organs, was only 16.7%. This one year survival was the same as in patients who had a resectable lesion but radical surgery was not performed because of the patient's refusal or poor general condition.

This indicates that resection of esophageal carcinoma of a_3 *lesions* has no treatment value. The preoperative diagnosis of an a_3 lesion is, therefore, of great importance in order to avoid a meaningless operation.

In the first part of the present study esophagograms and azygograms were evaluated as diagnostic aids to preoperatively differentiate between a_3 lesions and resectable ones.

Materials and Methods

Two hundred eight patients with carcinoma of the thoracic esophagus who underwent surgical resection during the period from 1965 to 1975 were studied. The patients ages ranged from 36 to 76 years; 173 were males and 35 were females were studied. The locations of the lesions are shown in Figure 1 and Table 1.

Esophagogram

A preoperative barium swallow study was performed by all 208 patients. Esophagograms were taken in three positions, posteroanterior position, left anterior oblique position and right anterior oblique position. A lesion appeared as a defect or abnormality and the length was measured on the films. The tumors were classified into six radiologic types[3] (Fig. 2): 1) superficial; 2) tumorous; 3) serrated; 4) funnelled; 5) spiral and 6) unclassified.

An analysis of the abnormalities of the "esophageal axis" was done by Akiyama's method,[1] and abnormal findings were classified into three types (Fig. 3):

---

* The pathohistologic status of esophageal carcinoma was divided into five stages according to "Guide Lines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus" proposed by Japanese Society for Esophageal Diseases.[3]

Reprint requests: Shozo Mori, M.D., Second Department of Surgery, Tohoku University Hospital, 1-1, Seiryo-Cho, Sendai, Japan.

Submitted for publication: June 22, 1977.

0003-4932/79/0700/0100 $00.95 © J. B. Lippincott Company

1) tortuosity of the proximal side of the tumor; 2) angulation of the esophageal axis and 3) deviation of the esophageal axis.

Azygogram

Preoperative azygography was performed on 139 of the patients. Azygography was performed in the following manner. At the nineth or tenth spinous process of the thoracic vertebra with the patient lying in prone position a puncture was made at the ninth or tenth spinous process of the thoracic vertebra with a bone marrow puncture needle. After ascertaining that the tip of needle was exactly in the bone marrow, 20 ml of 64.9% solution of methylglucamine salt of iodamide was injected for five seconds. Immediately preceeding completion of the injection an azygogram was taken. In most patients the azygogram was taken in two directions; postero anterior and lateral. The abnormalities shown on the azygogram were classified into the following three types (Fig. 4): 1) evident shift; 2) narrowing or irregularity of the wall and 3) obstruction.

TABLE 1. *Age, Sex and Location of Tumor*

	Male			Female			
Age	Iu	Im	Ei	Iu	Im	Ei	Total
<49	1	4	5	1	0	1	12
50–59	8	26	17	0	8	2	61
60–69	5	56	32	3	11	8	115
70>	1	11	7	0	0	1	20
Total	15	97	61	4	19	12	208

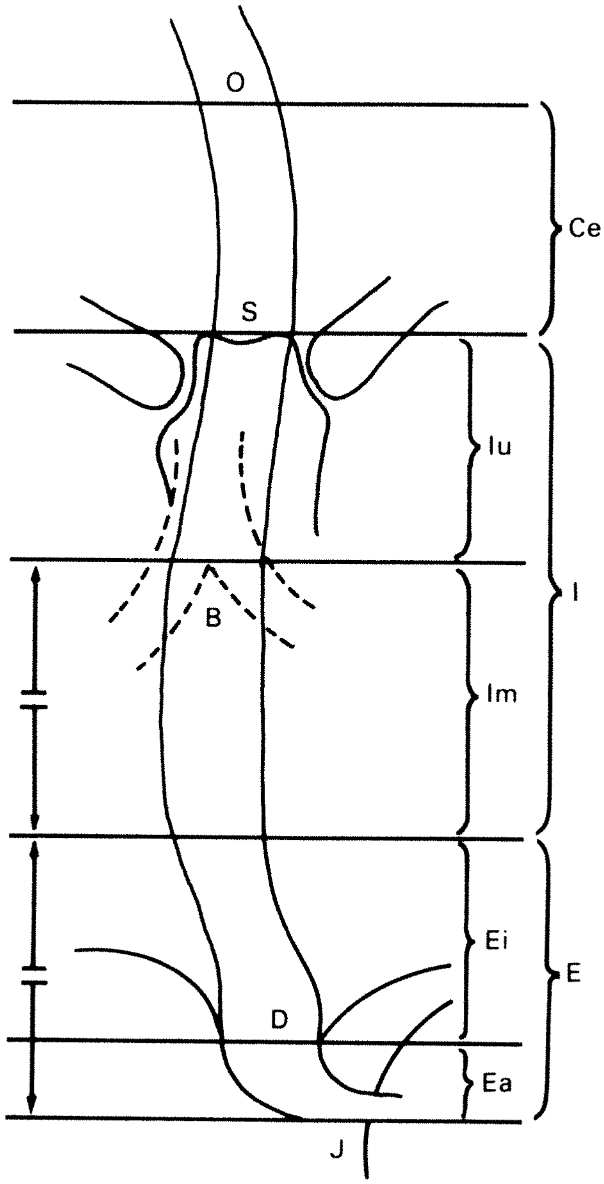


FIG. 1. Location of tumor. O: esophageal orifice. S: upper margin of the sternum. B: tracheal bifurcation. D: diaphragm. J: esophageal junction. Iu: upper intrathoracic esophagus between the levels of the upper margin of the sternum and the tracheal bifurcation. Im: middle intrathoracic esophagus, the proximal half of the esophagus between the tracheal bifurcation and the esophagogastric junction. Ei: lower intrathoracic esophagus, intrathoracic region of the distal half of the esophagus between the tracheal bifurcation and esophagogastric junction.

Histologic Examination

An histologic examination was made on all resected specimens. The depth of cancer invasion was classified into 4 groups in accordance with the "Guide lines for the clinical and pathologic studies on carcinoma of the esophagus:"[3]

a_0: No invasion into the adventitia
a_1: Invasion reaching the adventitia
a_2: Definite invasion into the adventitia
a_3: Invasion into the adjacent structures.

Lymph node metastases were also examined, and the carcinomas were classified according to stages (Table 2). The correlation between the degree of histologic carcinoma invasion and the findings of preoperative examinations were studied. The diagnostic value of these examinations for determining the operative indication was estimated.

Results

The pathohistologic stages of the patients are shown in Table 2. There were 33 patients with a_3 lesions. In ten patients radical resections could be performed by combined resection of neighboring organs such as a part of the lung, pericardium, thoracic duct or azygos vein (curative a_3). Palliative resections were performed

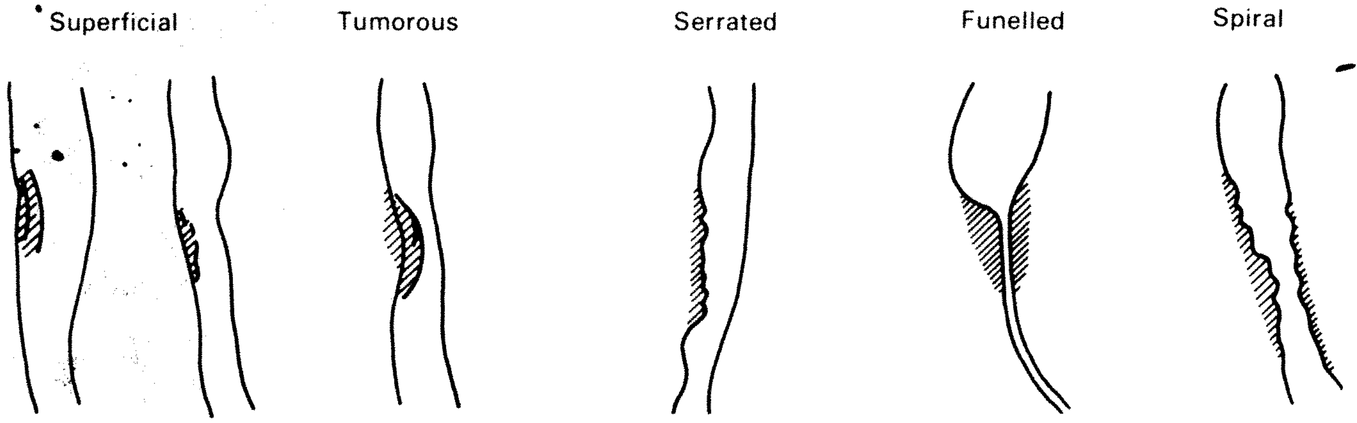


FIG. 2. Radiologic type of tumor.

on the remaining 23 cases with a_3 lesions (non-curative a_3).

Esophagogram

Tumor length. Table 3 shows tumor lengths as seen on x-rays. There were 107 patients (61.2%) with a lesion with the length of more than 6 cm among 175 cases with a_0–a_2 lesion. On the other hand, there were 29 cases (87.9%) with a lesion with the length of more than 6 cm among 33 cases with a_3 lesion. There were 19 cases with a_0–a_2 lesion among 26 having a lesion longer than 10 cm. Correlation between the length and depth of cancerous infiltration was not significant.

Radiologic type of tumors. (Table 4) There was no correlation between the type of tumor and depth of cancerous infiltration.

Deformity of esophageal axis. Abnormalities of esophageal axis were observed in 50 of the 208 patients (24.0%) as shown in Table 5. Abnormalities of esophageal axis were observed in 18.9% (33/175) of the patients with a_0–a_2 lesion and in 51.5% (17/33) of cases with a_3 lesion. There was a significant difference in the incidence of abnormalities of esophageal axis between a_0–a_2 cases and a_3 cases ($p < 0.001$). There were 16 a_3 cases without abnormalities of esophageal axis (false negative cases). In these cases the infiltration

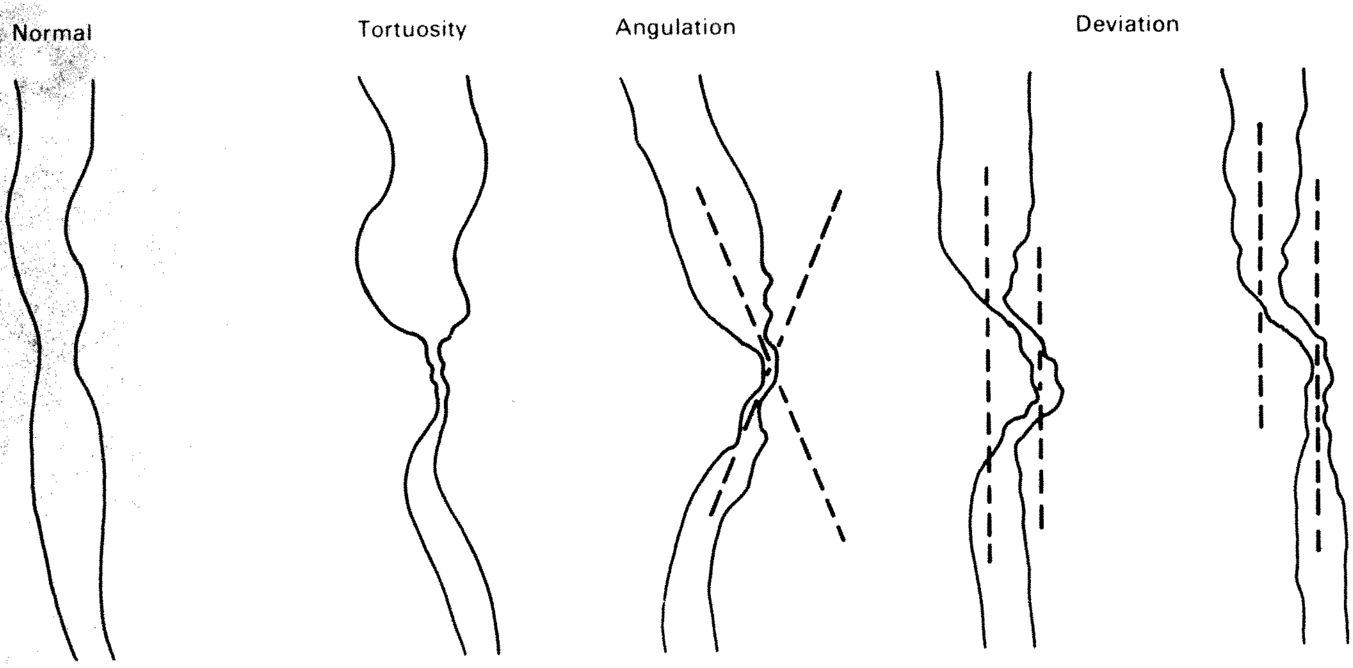


FIG. 3. Esophageal axis.

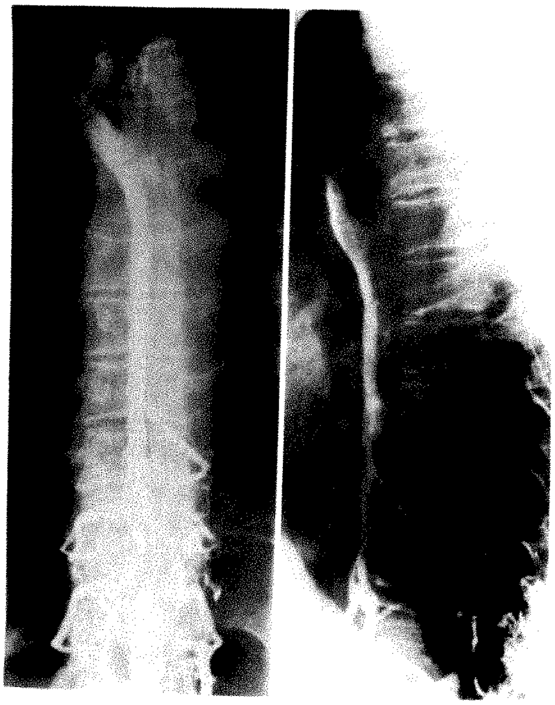


FIG. 4a. Normal azygogram.

was usually small and observed in lung or pericardium. Radical resections were possible with combined resection of infiltrated tissues in a half of these patients. There were 33 a_0-a_2 cases with abnormalities of esophageal axis (false positive cases). Twenty-eight patients (84.8%) had a past history of pulmonary tuberculosis, pneumonia or pleurisy. Twenty-seven of these patients had abnormalities such as calcification, pleural thickening of or disappearance of the costal sinus on chest x-rays. In ten of 33 false positive patients, inflammatory adhesion around carcinoma was observed at operation. In five patients abnormalities of esophageal axis were probably due to misinterpretation of the preoperative data by the investigators.

Azygogram

Abnormalities detected by the azygogram were observed in 26 (18.7%) of 139 patients examined, in 9.5% (11/116) of the patients with a_0-a_2 lesions and in 65.2% (15/23) of the patients with a_3 lesions (Table 6). There was a significant difference in the incidence of abnormal findings of azygograms between patients with a_0-a_2 lesions and patients with a_3 lesions ($p < 0.001$). There were eight patients with a_3 lesions who had a normal azygogram (false negative cases). In four patients the lesions occured in the upper intrathoracic esophagus distant from azygos vein. The lesions of the remaining four patients extended toward the left from azygos vein. On the other hand there were 11 a_0-a_2 patients with abnormal azygogram (false positive cases). Most had a past history of pulmonary tuberculosis, pneumonia or pleurisy and showed abnormalities on their chest x-rays such as calcification or pulmonary scarring.

Discussion

Since there has been no examination for the preoperative assessment of mediastinal lymph nodes

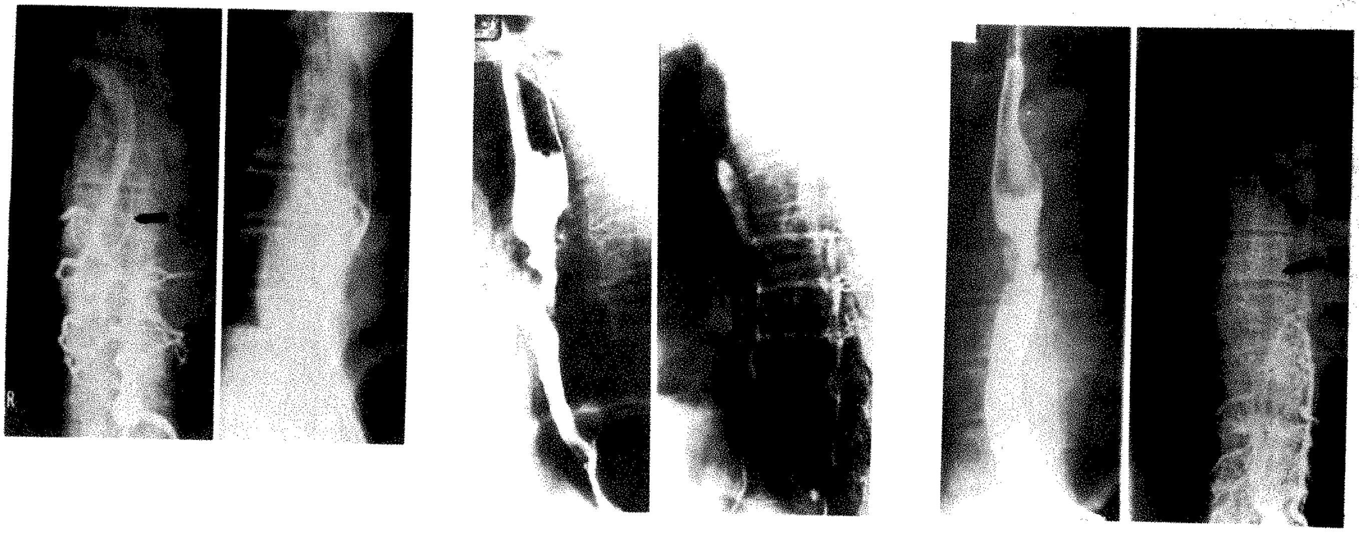


FIG. 4b. Abnormal azygogram. (Left) shift. (center) narrowing. (right) obstruction.

TABLE 2. *Histologic Depth of Invasion and Histologic Stage*

Depth of Invasion	Histologic Stage 0	I	II	III	IV	Total
a_0	4	20	1	7	12	44
a_1	0	0	19	6	9	34
a_2	0	0	0	67	30	97
a_3	0	0	0	0	33	33
Total	4	20	20	80	84	208

TABLE 4. *Type of Tumor and Depth of Invasion*

Depth of Invasion	Radiologic Type of Tumor: Superficial	Tumorous	Serrated	Funneled	Spiral	Total
a_0-a_2	4	16	45	72	38	175
a_3	0	1	6	15	11	33
Total	4	17	51	87	49	208

metastases, determination of preoperative curative resectability of esophageal carcinoma has been attempted by many investigators in connection with local extent. The length of the tumor on esophagogram has been considered as a useful parameter in deciding the operative indication. A tumor of 6 cm or less in length indicates a candidate for curative resection.[4] Our results indicated that tumor length, by itself, did not seem to be an adequate parameter for deciding resectability. The radiologic type of tumor had no value in the determination of operative indication. Akiyama studied the esophageal axes of 82 patients with esophageal carcinoma and showed that a preoperative prediction about resectability could be obtained by this study.[1] The esophageal axis was examined in 208 patients with esophageal carcinoma in the present series. Our results indicated that this examination was more useful than radiologic evaluation of the length and type of tumor in preoperative assessment of resectability. If we made a diagnosis of a_3 (both curative a_3 and noncurative a_3) of a patient with an esophageal axis abnormality, the probability of a correct diagnosis was 76.4% (159/208). The probability of only noncurative a_3 was 79.3% (165/208). There were 16 false negative cases and 33 false positive cases. From an analysis of the 33 false negative cases it was shown that abnormalities of esophageal axis were also caused by adhesion of the esophagus to the surrounding tissues due to previous inflammation of pleura, lung or esophagus, or reactive inflammation around the tumor. Another cause of misdiagnosis was misinterpretation of the data by investigators. The a_3 cases in which infiltration was restricted to the small area of the lung or pericardium revealed a normal esophageal axis. Many patients underwent curative resection with combined resection of the infiltrated tissue.

Azygography had been studied by many investigators regarding operative indication for pulmonary carcinoma or mediastinal tumor.[2,5] We have studied the azygography of patients with esophageal carcinoma from 1961 to 1964.[6] Azygography was performed on 139 patients with carcinoma of the thoracic esophagus in the present series, and the usefulness of azygography for preoperative assessment of resectability was confirmed. If we made a diagnosis of a_3 (both curative and noncurative a_3) in patients with abnormal azygogram, the probability of correct diagnosis was 86.3% (120/139). The probability of only noncurative a_3 was 85.6% (119/139). The examination of azygograms gave more accurate information about resectability than esophageal axis examination. The causes of misdiagnosis in azygogram were similar to those in the esophageal axis. The findings of the azygogram were influenced by the past or present existence of inflammation arround the azygos vein which occasionally led to misdiagnosis. Tumor location and the direction of carcinomatous growth were also causes of misdiagnosis, but they were not of great importance because there were not many cases in which the carcinoma occupied the upper intrathoracic esophagus and most carcinomas with a_3 lesions cases developed in whole directions. While the azygogram and esophageal axis findings gave useful information about resectability, combination of the findings with some other above mentioned diagnostic procedures seemed to be required

TABLE 3. *Length of Tumor and Depth of Invasion*

Depth of Invasion	Length of Tumor on X-ray Film (cm): <3.9	4.0–5.9	6.0–7.9	8.0–9.9	10.0>	Total
a_0-a_2	12	56	57	31	19	175
a_3	0	4 (2)	13 (7)	9 (9)	7 (5)	33 (23)
Total	12	60 (2)	70 (7)	40 (9)	26 (5)	208 (23)

Numbers in parentheses indicate noncurative a_3.

TABLE 5. *Esophageal Axis and Depth of Invasion*

Depth of Invasion	Normal Axis	Abnormal axis: Tortuosity	Angulation	Deviation	Total
a_0-a_2	142	4	13	16	175
a_3	16 (8)	1 (1)	10 (8)	6 (6)	33 (23)
Total	158 (8)	5 (1)	23 (8)	22 (6)	208 (23)

Numbers in parentheses indicate noncurative a_3.

TABLE 6. *Azygogram and Depth of Invasion*

Depth of Invasion	Normal Azygogram	Abnormal Azygogram			Total
		Shift	Narrowing Irregularity	Obstruction	
a_0–a_2	105	3	3	5	116
a_3	8 (5)	0	8 (6)	7 (5)	23 (16)
Total	113 (5)	3	11 (6)	12 (5)	139 (16)

Numbers in parentheses indicate noncurative a_3.

in order to avoid erroneous interpretation by a single method. By so doing a more accurate preoperative determination of surgical indications is possible for carcinoma of the esophagus.

References

1. Akiyama, H., Kogure, T., and Itai, Y.: The Esophageal Axis and its Relationship to the Resectability of Carcinoma of the Esophagus. Ann. Surg., 176:30, 1972.
2. Bachman, A. L., et al.: Azygography, its Value in Mediastinal Adenopathy and Tumors. Ann. Surg., 153:344, 1961.
3. Japanese Society for Esophageal Diseases: Guide Lines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus. Jap. J. Surg., 6:69, 1976.
4. Nakayama, K., and Hirota, K.: Experience of About 3000 Cases with Cancer of the Esophagus and the Cardia. Aust. N. Z. J. Surg., 31:222, 1962.
5. Schwartz, S., et al.: Azygography. Radiology, 72:338, 1959.
6. Takahashi, Y.: Experimental and Clinical Study on Azygography with Special Reference to the Determination of Operative Indication of the Carcinoma of the Esophagus. J. J. A. T. S., 12:102, 1964.

The Effects of Hypothermia on Myocardial Oxygen Consumption and Transmural Coronary Blood Flow in the Potassium-arrested Heart

W. RANDOLPH CHITWOOD, JR., M.D., JAMES D. SINK, M.D., RONALD C. HILL, M.D.,
ANDREW S. WECHSLER, M.D., DAVID C. SABISTON, JR., M.D.

From The Department of Surgery, Duke University Medical Center, and the Veterans Administration Medical Center, Durham, North Carolina

Hypothermia remains the primary adjunct employed to lower cellular metabolism during various cardiac procedures. In these experiments, left ventricular myocardial oxygen consumption (MVO_2) and transmural blood flow (TBF) were measured during cardiopulmonary bypass with the range of temperatures used clinically. Determinations were made in empty beating normothermic hearts and after potassium cardioplegia at 37, 32, 28, 22, 18, and 15° ($K^+ = 15-37$ meq/L: Hct 25 volumes %). Oxygen content of the total coronary sinus collection was compared with a large volume arterial sample using a Lex-O_2-Con-TL analyzer (vs Van Slyke, $R = 0.98$). Transmural blood flow was measured at each temperature using microspheres (8μ), and perfusion was maintained at 80 mmHg. Asystole (37°) alone decreased MVO_2 from 5.18 ± 0.55 to 1.85 ± 0.20 ml O_2/min/100 g of left ventricle or approximately 65% ($p < 0.001$). With progressive cooling to 15° an additional 82% decrement in oxygen uptake occurred during asystole ($p < 0.001$). During asystole at 37° the decrease in MVO_2 was reflected mainly by a large decrement ($p < 0.01$) in TBF (1.27 ± 0.19 to 0.74 ± 0.17 ml/min/g of mean left ventricular flow). However, with cooling below 32°, the arteriovenous oxygen difference narrowed progressively ($p < 0.001$) while TBF paradoxically returned to control levels. Endocardial/epicardial flow ratios were not altered by cooling. These data not only confirm earlier reports describing a sequential drop in MVO_2 with incremental myocardial cooling, but also establish MVO_2 levels for perfused hearts arrested by potassium at lower temperatures (18–15°). Moreover, as transmural blood flow becomes independent of metabolic necessity during hypothermia, coronary autoregulation appears to be impaired, possibly affecting detrimental tissue over perfusion.

MAINTENANCE OF MYOCARDIAL FUNCTION and structural stability is highly dependent upon oxygen availability for specific cellular oxidative pathways. Interruption of coronary blood flow results in a rapid expenditure of myocardial oxygen reserves with secondary depletion of high-energy phosphate stores, which are necessary to maintain multiple intracellular processes.[7,20,24] In adequately perfused hearts, myocardial oxygen consumption has remained an accurate quantitative indicator of cellular respiratory and metabolic activity.[15,28] Moreover, it is a sensitive method for analyzing myocardial energetics without inducing irreparable organ damage that generally occurs after multiple cardiac biopsies.

Sir Joseph Barcroft first determined oxygen consumption in beating and arrested mammalian hearts at Cambridge in 1906.[5] Since then, numerous metabolic and mechanical factors have been shown to affect oxygen uptake directly in beating as well as in both fibrillating and arrested hearts.[8,15,28,37] During operations necessitating cardiopulmonary bypass, the advantage of minimizing depletion of specific high-energy phosphate stores has been expressed widely for a number of years.[1,16,17,36,38] Numerous methods have been employed to achieve cellular preservation to assure optimal postoperative ventricular function. The overall objective of myocardial protection during many cardiac operations has been to minimize residual oxygen demands, especially during periods of diminished blood supply. Cardiac cooling has been shown to be most effective in decreasing cellular activity both in isolated as well as in *in vivo* preparations.[9,13,14,38] Various reports have detailed cardiac oxygen consumption during hypothermic cardiopulmonary bypass.[2,4,9] However, none have comprehensively determined oxygen uptake over the entire range of temperatures (37–15°) used clinically, and this is especially true for vented pharmacologically arrested hearts. Moreover, data comparing myocardial

---

Reprint requests to: W. Randolph Chitwood, Jr., M.D., Box 3025, Duke University Medical Center, Durham, North Carolina 27710.

This study was supported in part by NIH Grants 5-RO1-HL-09315-14 and HL-07101.

0003-4932/79/0700/0106 $01.05 © J. B. Lippincott Company

demands with relative oxygen supply in perfused hearts remains incomplete for markedly lower temperatures.

Methods

Eleven adult mongrel dogs (18–27 kg) were evaluated for left ventricular oxygen consumption and transmural myocardial blood flow during asystolic cardiopulmonary bypass conditions at commonly used levels of clinical hypothermia.

Cardiopulmonary Bypass Preparations

The animals were anesthetized with pentobarbital (30 mg/kg), intubated, and ventilated with the use of a model 607 Harvard mechanical respirator (FIO$_2$ 40%). Arterial blood gases prior to cardiopulmonary bypass were Po$_2$ 134 ± 18 mmHg, Pco$_2$ 25 ± 5 mmHg, and pH 7.47 ± 0.02, while the hematocrit was 38 ± 2 volumes per cent concurrently. A median sternotomy was performed and polyvinyl chloride catheters (14G) measured coronary perfusion, systemic and left ventricular intracavitary pressures throughout each experiment with the use of synchronously calibrated model 1280 Hewlett-Packard pressure transducers (Fig. 1). A left subclavian arterial cannula (16G) was placed to obtain reference samples for microsphere flow determinations. To confirm maintenance of asystole, ventricular epicardial electrodes monitored electrocardiographic activity continuously. During each study, transmural temperatures were measured by means of intramyocardial microthermistor probes* inserted into the anterior ventricular wall. Coupled Wheatstone bridges were previously calibrated in 2° increments between 40° and 15° employing a variable temperature bath. All physiologic data were recorded by a Hewlett-Packard model 7758-A 8-channel direct writing oscillograph (25 mm/sec) and model 8805-C pressure amplifiers.

Heparin (200 μ/kg) was administered intravenously, and femoral arterial perfusion was instituted by means of a Harvey bubble oxygenator (H-1000) primed with 2 l hemodiluted heparinized donor blood (25 ± 1 vol.%). Both the inferior and the superior vena cavas were cannulated for venous drainage *via* the right atrium, and the azygos vein was ligated securely (Fig. 1). Throughout each study, a large apical vent decompressed the left ventricle to 0 mmHg. Normothermic (37°) systemic perfusion was stabilized at 80 mmHg (flow 50–150 ml/min/kg). Within the first 10 minutes of bypass, the left carotid artery was cannulated independently, and the descending aorta was then clamped. Separate coronary perfusion was maintained continuously at 80 mmHg by a Cole Parmer No. 7565 roller pump, equipped with an interposed heat-exchanging coil designed to deliver hypothermic flow. Adequate cerebral perfusion (60–80 mmHg) was provided by a separate polyvinyl chloride systemic-carotid shunt.

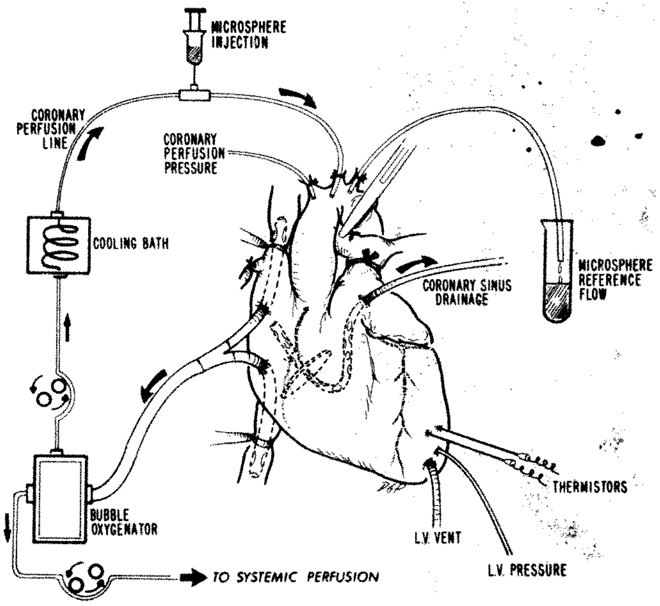


FIG. 1. Diagram of cardiopulmonary bypass technique used during this study. Independent aortic arch perfusion was provided by carotid cannulation which enabled selective cardiac cooling. Total coronary venous effluent was collected from the right ventricular outflow tract and isolated right atrium. An apical vent maintained intracavitary pressures at 0 mmHg. Microthermistors measured anterior wall endocardial and epicardial temperatures. Additional catheters determined microsphere reference flow as well as simultaneous left ventricular, systemic, and coronary perfusion pressures.

A large cannula with multiple perforations was inserted subsequently through the right ventricular outflow tract, across the tricuspid valve, and into the right atrium. After the main pulmonary artery had been ligated, all coronary sinus and thebesian drainage was diverted into a large separatory funnel (2l) by gravity flow. Samples were collected under a layer of mineral oil to avoid any contact with air. After aortic arch isolation, total coronary venous drainage remained within 10% of coronary arterial pump inflow. During each coronary venous collection, a similar volume of arterial blood was obtained in a separate anaerobic container.

Following initial *empty* beating determinations, systemic hyperkalemia brought about ventricular asystole, which was sustained throughout the experimental period by supplemental additions of potassium chloride to the oxygenator. Perfusate potassium levels range between 15 and 37 mEq/l (mean 32 ± 9 mEq/l) as measured by a calibrated model 143 IL

---

* Model 524, Yellow Springs Instrument Company.

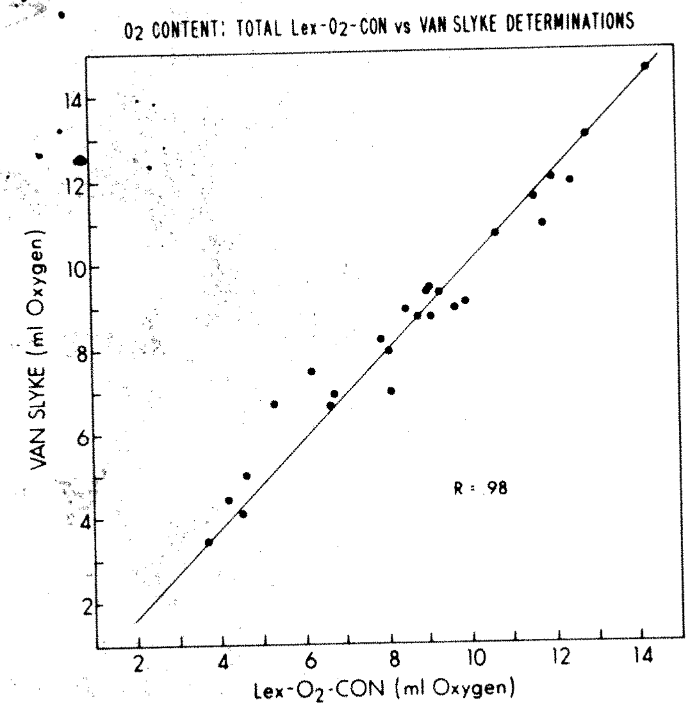


FIG. 2. Total oxygen content was determined by the Van Slyke-Neill method and compared to values obtained using a Lex-O_2-Con-TL oxygen analyzer. Twenty-six samples, including coronary sinus (N = 9), arterial (N = 9), and mixed venous (N = 8) blood were evaluated by both methods and statistically compared by regression analysis ($r = 0.98$; $y = 0.94x + 0.53$).

flame photometer.* During the bypass interval (100–160 min), the oxygenator Po_2 averaged 320 ± 30 mmHg while the pH was maintained at 7.47 ± 0.02 by adding sodium bicarbonate when necessary. No pharmacologic agents were used to alter blood pressure during this study.

Myocardial Oxygen Consumption

For each MVO_2 determination, total coronary venous flow was collected over ten minutes and compared to a similar volume of arterial blood. Each unit was carefully mixed, avoiding any air interface. For oxygen analysis three 5 ml aliquots were withdrawn from each collection in mercury-sealed syringes. All samples were evaluated in triplicate for oxygen content (volumes per cent), using a Lex-O_2-Con-TL oxygen analyzer† validated previously by the method of Van Slyke and Neill.[34] Multiple temperature and barometric pressure corrections were made throughout each study, and calibration of the Lex-O_2-Con-TL was considered optimal if three consecutive readings for dry air were within ± 0.1 volumes %.[11,35] Linear regression analysis comparing Van Slyke-Neill values with Lex-O_2-Con-TL determinations provided a correlation coefficient of 0.98 with an equation of $y = 0.94x + 0.53$ for 26 blood samples compared collectively (Fig. 2). When evaluated individually, arterial (N = 9), coronary sinus (N = 9), and mixed venous blood (N = 8) showed comparable values of r = 0.97, 0.98, and 0.84 respectively.

At the termination of these studies each heart was extirpated, blotted dry, and both right and left ventricles were weighed separately. Myocardial oxygen consumption (ml O_2/min/100 g of left ventricle) was then determined by the formula:

$$MVO_2 = \frac{[A-V\ O_2 \times Q_{cv}]}{LV\ wt.} \times 100$$

A–V O_2,	difference between arterial and coronary venus oxygen content (volumes %; ml O_2/100 ml blood)
Q_{cv},	coronary venous blood flow (ml/min)
LV wt.,	left ventricular wet weight in grams

Myocardial Blood Flow

Regional myocardial blood flow was measured at each temperature level using 8- to 10-μ microspheres‡

---

* Instrumentation Laboratory, Inc., Boston, Massachusetts.

† Lexington Instruments, Waltham, Massachusetts.

‡ 3M Manufacturing Company, Minneapolis, Minnesota.

TABLE 1. *Myocardial Oxygen*

	Empty Beating Heart 37° (control)	p*	37°	p*	p	32°
Coronary venous flow (ml/min)	167 ± 16	0.001	77 ± 11	0.03	NS	103 ± 23
A–V O_2 difference† (volumes %)	4.28 ± 0.42	NS	3.92 ± 0.43	0.001	0.005	1.14 ± 0.22
MVO_2‡ (ml O_2/min/100 g L.V.)	5.18 ± 0.55		1.85 ± 0.20			0.82 ± 0.11
p (MVO_2)		0.001		0.005		

Left ventricular oxygen consumption (MVO_2), coronary venous flow, and coronary arteriovenous oxygen differences are represented for temperatures between 37° and 15°C. After empty beating normothermic control determinations, hearts remained asystolic for the remainder of the study.

p represents comparisons between specific interventions.

* p compares each intervention to control. Statistical significance, $p < 0.05$. NS: not significant. Data are mean ± standard error of the mean.

† A–V O_2 diff., difference between arterial and coronary venous oxygen content.

‡ MVO.

labeled with either ^{125}I, ^{141}Ce, ^{54}Cr, ^{85}Sr, or ^{46}Sc. Determinations were performed by means of injection techniques validated previously for similar experimental bypass conditions.[10] Less than 1% of injected microspheres were measured in the coronary venous effluent, an indication of almost total myocardial entrapment. After excision, ventricles were weighed separately and immersed in 10% buffered formalin for 5–7 days. Following fixation, epicardial fat and large superficial vessels were removed. A midventricular ring was divided into five regions: 1) anterior wall, 2) anterior papillary, 3) lateral wall, 4) posterior papillary, and 5) posterior wall. Each regional piece was sectioned into epicardial, outer myocardial, inner myocardial, and subendocardial layers of equal thickness. A thin transmural slice was included to define mean transmural blood flow for each region. Tissues were weighed separately and were quantitatively analyzed for gamma radioactivity in a Beckman Biogamma Counter. After background subtraction and correction for spectral energy overlap, myocardial blood flow in milliliters per minute per gram was determined by the method of Rudolph and Heyman.[33]

Data Collection

Both oxygen consumption and regional transmural blood flow were obtained for each left ventricle at specific periods during the cardiopulmonary bypass interval. After 15 min of stable bypass perfusion (37°), ten minute blood collections were initiated for *empty beating* MVO_2 determinations. An injection of microspheres was made concurrently to assess transmural blood flow in these normothermic vented hearts (N = 11). After arrest was established by systemic hyperkalemia, collections were made again during normothermic *asystole*. Animals were then divided into two groups for subsequent hypothermic determinations to obviate unphysiologic bypass times. In Group I (N = 6) both transmural blood flow and MVO_2 data were obtained during asystole at 32°, 22°, and 15°, and in Group II (N = 5) similar determinations were made at 28° and 18°. The temperature sequence was varied randomly to optimize accuracy. Subendocardial temperatures were maintained within ± 1° of desired levels for five minutes before any blood collections were initiated.

Student's t test for paired and unpaired data was used to establish statistical significance ($p < 0.05$) for both MVO_2 and blood flow data. Values are expressed as mean ± standard error of the mean (±SEM). All statistical tests, microsphere flow determinations, and regression analyses were performed using IBM 1130 digital computer programs.

Results

Data are represented for 11 animals (5 males and 6 females) that underwent a cardiopulmonary bypass study without complicating technical problems. Before extracorporeal perfusion was instituted, anesthetized open-chest preparations had average heart rates of 137 ± 4 beats/minute and aortic blood pressures of 115 ± 5/84 ± 5 mmHg. Left ventricular pressures averaged 115 ± 5/4 ± 1 mmHg simultaneously. After bypass was initiated, intracavitary pressures of vented empty beating ventricles (37°) remained continuously at 0 mmHg with a mean heart rate of 135 ± 4 beats/min.

Myocardial Oxygen Consumption

Coronary arteriovenous oxygen differences, coronary venous blood flow, and myocardial oxygen consumption at each temperature level are shown in Table 1 and in Figures 3 and 4. Normothermic pharmacologic arrest alone affected a nearly 65% decrease in oxygen consumption (5.18 ± .55 to 1.85 ± 20 ml O_2/min/100 g LV). Ablation of electromechanical activity did not induce a concomitant fall in oxygen extraction at normothermia (Fig. 4). However, at the same time, a notable reduction in coronary blood flow (coronary

Consumption (MVO_2)

Asystole											
p*	p	28°	p*	p	22°	p*	p	18°	p*	p	15°
NS	NS	148 ± 28	NS	NS	120 ± 27	NS	NS	131 ± 22	0.03	NS	110 ± 21
0.001	NS	0.89 ± 0.17	0.001	NS	0.73 ± 0.22	0.001	NS	0.55 ± 0.20	0.001	NS	0.42 ± 0.14
		0.72 ± 0.18			0.54 ± 0.05			0.40 ± 0.08			0.33 ± 0.05
		0.04						0.01			

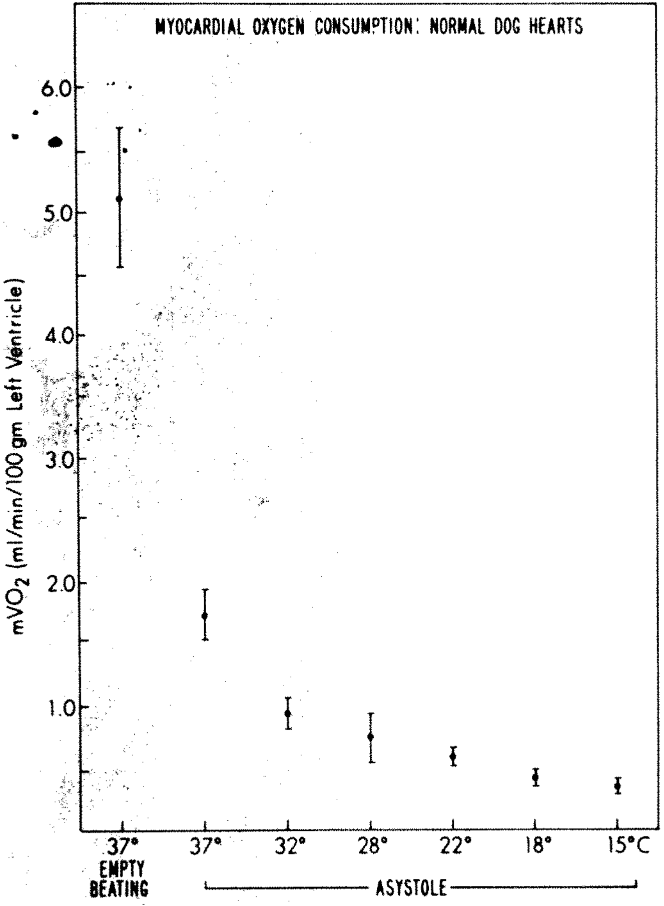


FIG. 3. Myocardial oxygen consumption (MVO_2) was determined for 11 dog hearts during empty beating normothermic conditions and following potassium arrest at several temperature levels (37°–15°C).

sinus $p < 0.001$; microsphere $p < 0.05$) did occur, reflecting these markedly decreased oxygen requirements (Tables 1 and 2). By cooling asystolic hearts to 32°, an additional 55% decrement in MVO_2 developed ($p < 0.005$). A nearly linear decline in oxygen consumption existed at ventricular temperatures between 28 and 15° (Fig. 3). Regression analysis comparing the logarithm of myocardial oxygen consumption in asystolic hearts to each temperature investigated (Fig. 5) revealed a correlation coefficient of $r = 0.83$ and the equation, $\log y = 0.033x - 1.04$, where $y = MVO_2$ (ml O_2/min/100 g LV) and x = temperature in centigrade.

With progressive cooling, the arteriovenous difference narrowed, indicating decreasing oxygen extraction from the coronary perfusate (Fig. 4). At 15° myocardial oxygen consumption was approximately 0.33 ml O_2/min/100 g or about 82% less than that of completely asystolic hearts at 37°. Thus, during total electromechanical arrest, a significant decline in oxygen demand continues below 32° with each 7–10° of perfusion cooling. This effect represents a Q_{10} of 1.6 or approximately a 45% decline in myocardial oxygen uptake for each 10° of cooling.

Myocardial Blood Flow

Prior to fixation, right and left ventricular wet weight averaged 34.5 ± 2.5 and 120.0 ± 6.2 g, respectively. Transmural myocardial blood flow for each temperature is presented in Table 2 and Figure 6. Blood-flow data are shown only for the anterior papillary region; however, no statistical difference existed between values from this area and other myocardial regions.

After initiating asystole at 37° and during hypothermic perfusion, endocardial:epicardial flow ratios were never statistically altered from control values (Fig. 7). In comparison, by decreasing oxygen requirements through pharmacologic arrest, the epicardial, endocardial, and mean transmural blood flows each became markedly attenuated at 37° ($p < 0.05$). After continued cooling to below 32°, myocardial blood flow became augmented to each transmural ventricular layer (Fig. 6). At temperatures between 22 and 15°, epicardial and outer myocardial blood flow even increased to greater than control levels ($p < 0.05$). At the same time mean transmural blood flow returned to empty beating control levels in all regions (Table 2).

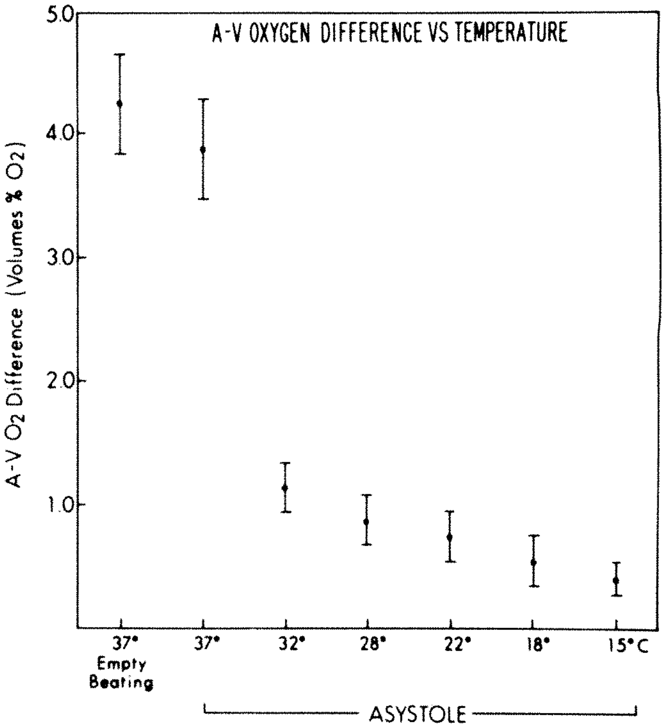


FIG. 4. Coronary arteriovenous O_2 differences in volumes per cent are compared at each temperature investigated. The A–V difference narrowed, indicating progressively decreasing myocardial oxygen extraction with cooling.

curred compared with that in normothermic arrest alone. Further cooling to 15° decreased oxygen consumption to 0.33 ml/O_2/min/100 g, which was 6% of that used by empty beating normothermic ventricles (Fig. 3). These results are similar to measurements from isolated rat heart slices in which Fuhrmann et al. showed a nearly 80% drop in oxygen consumption after cooling from 37° to 15°.[13] The present data conform to Van Hoft's law for most living systems, a finding which suggests that each 10° of hypothermia reduces tissue metabolic activity by about 50%.[4,16,21,22] This linear relationship is shown in Figure 5 where the logarithm of oxygen consumption is compared with decreasing temperature levels for asystolic hearts ($Q_{10} = 2.1$).

Ventricular cooling appears necessary to achieve minimal energy requirements and thus maximal ventricular protection during cardiac operations. Rendering the heart asystolic alone does not inhibit myocardial activity sufficiently to afford optimal cellular preservation.[16,17] At markedly lower temperatures (15°) during pharmacologic arrest, interrupted coronary inflow still results in reduced high-energy phosphates.[24,38] This is especially true during prolonged periods of ischemia when myocardial phosphate stores are more extensively depleted. Jennings et al. recently reported that 93% of available ATP is depleted after 40 minutes of *normothermic* ischemia, and the magnitude of cellular damage generally depends on the overall level of phosphate exhaustion.[20] During prolonged ischemic conditions, specific precursors are lost from the total nucleotide pool (ATP, ADP, and AMP), often eventuating in irreparable contractile function and cellular necrosis. Although glycolytic ATP may be available during early ischemic periods, rapid accumulation of cellular metabolites occurs and may additively inhibit effective utilization of metabolic substrates, even during profound hypothermia.[24] Myocardial cooling definitely impedes ATP expenditure during ischemia; however, excessive periods of interrupted inflow continue to result in irreversible cell damage.

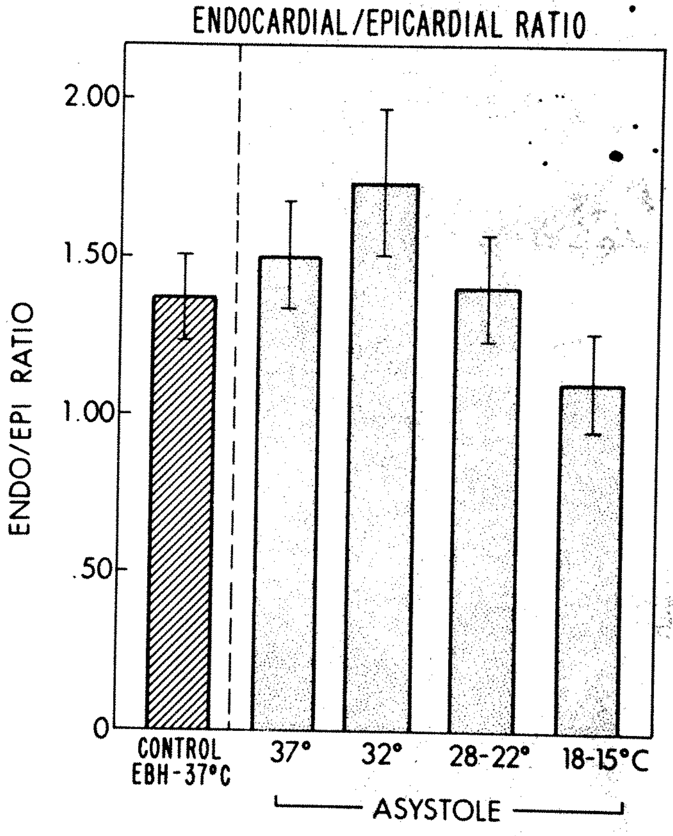


FIG. 7. Endocardial:epicardial flow ratios are compared at various temperature levels. Flow ratios were not statistically altered by either pharmacologically arresting or cooling these hearts from 37°C to 15°C.

These studies emphasize the magnitude of myocardial oxygen deprivation which accompanies global cardiac ischemia. By maintaining perfusion, data have been derived that now allow determination of cellular oxygen requirements in arrested hearts during any period of coronary inflow ablation at various temperatures. Oxygen uptake for actively working dog hearts at normothermia for an 18 minute period totals between 140 and 180 ml.[28] Ventricles undergoing longer ischemic periods have been shown to develop irreversible cellular damage.[19] In comparison, by cooling asystolic hearts to 15°, the oxygen requirement for one hour is 19.8 ml. Even though this cumulative oxygen debt is significantly less than that accrued by the working dog heart model, noticeable myocardial injury still occasionally occurs in clinical situations during similar periods of ischemic arrest. Therefore, a relationship probably exists between the duration of ischemia and myocardial damage that is not totally dependent on the overall oxygen debt incurred.

Despite markedly decreased oxygen expenditure, coronary blood flow became paradoxically augmented in these asystolic hearts at successively lower temperatures (Figs. 8 and 9). Although arteriovenous oxygen extraction and MVO_2 were lowest at 15°, coronary blood flow was maximal. Therefore, myocardial perfusion at lower temperatures appears to become independent from cellular requirements, an indication of impaired coronary autoregulation. Hypothermia has previously been shown to produce coronary vasodilation in beating hearts[2,6,18,27]; however, in asystolic preparations, compressive forces of contraction are removed and full impact of cooling on coronary vasomotion becomes even more evident. At lower

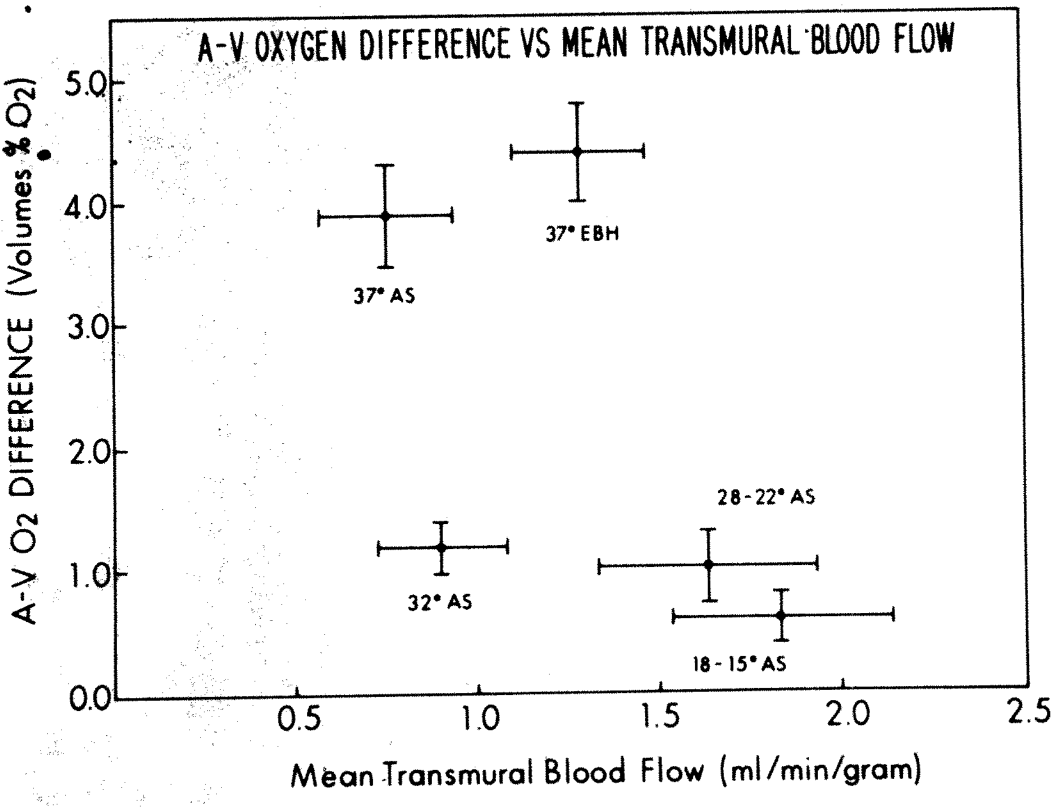


FIG. 8. Coronary arteriovenous oxygen differences are compared with simultaneous mean transmural blood flow levels. Arteriovenous oxygen difference narrowed significantly below 37°C while mean transmural blood flow became augmented. EBH, empty beating heart; As, asystole; temperature, °C.

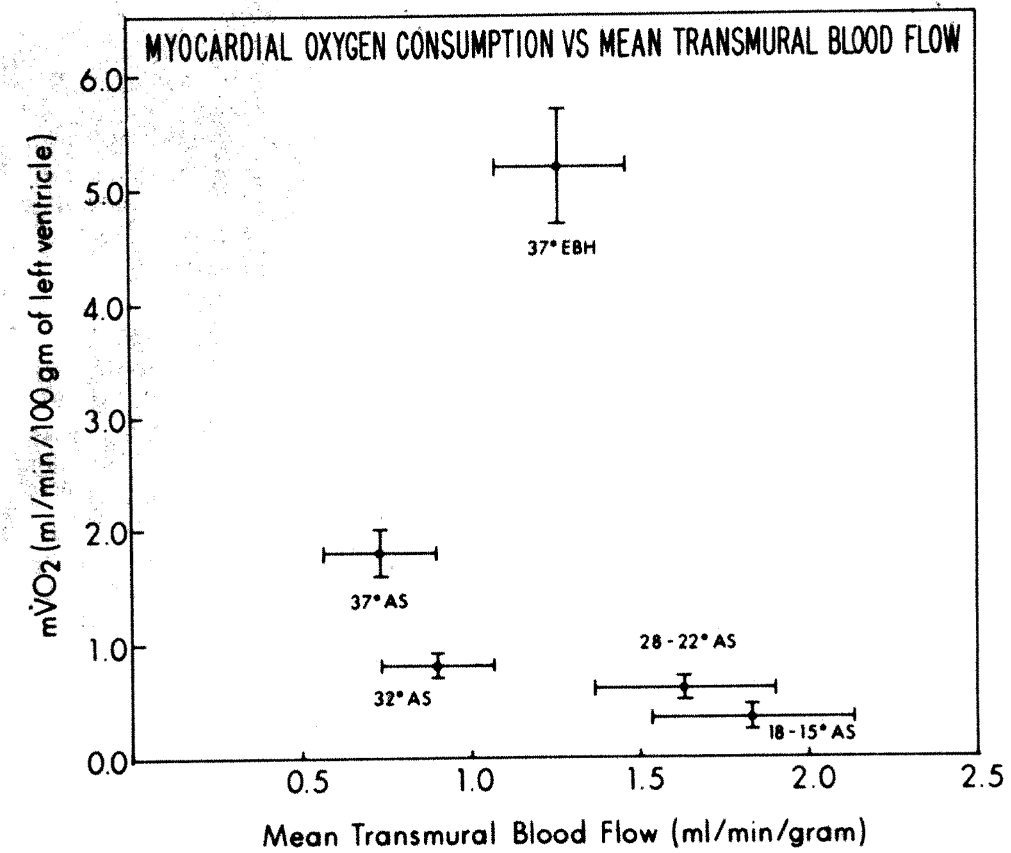


FIG. 9. Myocardial oxygen consumption is compared with mean transmural blood flow values at specific experimental temperatures. Flow paradoxically increased while ventricular oxygen demand declined. EBH, empty beating heart; As, asystole; temperature, °C.

Throughout the experimental protocol, coronary venous flow responses generally paralleled microsphere flow determinations (Table 1). During control empty-beating normothermic conditions, coronary venous drainage was 167 ± 16 ml/min. After induction of asystole, venous flow dropped by 54% ($p < 0.001$), but became re-established at control levels when 28° was reached. No statistical difference existed in coronary venous flow between 18° and normothermic control levels. However, a slight decrement in coronary sinus outflow again became evident at 15°.

Discussion

Oxygen consumption has become an established method for evaluating cellular metabolic activity in living tissues.[8,15,37] In the beating, working heart the primary factors which influence oxygen utilization are transmural wall tension of the ventricle, intrinsic contractile state of the myocardium, and the heart rate.[8,28] Processes that necessitate oxygen usage and remain significant, especially during interrupted coronary blood flow, include transcellular ion exchange, cell volume regulation, and membrane stability.[8,20] Each of these cellular functions is particularly vulnerable during operations requiring cardiopulmonary bypass. Thus, most surgeons attempt to minimize intraoperative myocardial oxygen demands to conserve high-energy phosphate stores.

Specific protective measures are employed during clinical bypass procedures in an attempt to decrease these intracellular metabolic demands and to optimize functional recovery. Such techniques include ventricular venting, adrenergic blockade, pharmacologic cardioplegia, and hypothermia.[1,9,29,31,38] Immediate arrest utilizing potassium cardioplegia has been supported widely as it markedly decreases myocardial oxygen requirements by eliminating all cellular contraction in a totally flaccid heart.[1,29,36] Numerous reports have defined oxygen consumption at various levels of hypothermia with both *in vitro* and *in vivo* preparations.[2,4,9,13,14,21,22,26,30] In no single experiment, however, has myocardial oxygen consumption been evaluated as a variable independent from changes in heart rate and rhythm throughout the range of temperatures used clinically.

In the present experiments, oxygen consumption of the vented beating left ventricle (37°) was 5.18 ± .55 ml O_2/min/100 g, a value consistent with those in most other reports.[2,9] In contrast, actively working hearts generally have been shown to consume between 8 and 10 ml of oxygen per 100 g of left ventricle even though much experimental variability exists.[8,15,28] After the onset of normothermic asystole, myocardial oxy-

TABLE 2. *Transmural Myocardial Blood Flow (ml/min/gram)*

Transmural Layer	Empty Beating Control 37°		Asystole																
		p*	37°	p*	p	32°	p*	p	28°	p*	p	22°	p*	p	18°	p*	p	15°
Epicardium	1.04 ± 0.15	0.02	0.56 ± 0.11	0.05	NS	0.61 ± 0.08	NS	0.05	1.51 ± 0.40	NS	NS	1.44 ± 0.29	0.04	NS	1.69 ± 0.32	0.05	NS	1.72 ± 0.51
Outer myocardium	1.04 ± 0.14	0.01	0.55 ± 0.11	0.05	NS	0.66 ± 0.10	0.05	0.03	1.88 ± 0.50	0.05	NS	1.71 ± 0.41	0.04	NS	1.81 ± 0.41	0.04	NS	1.95 ± 0.53
Inner myocardium	1.40 ± 0.20	0.03	0.74 ± 0.18	NS	NS	0.99 ± 0.14	NS	0.05	2.12 ± 0.51	NS	NS	1.95 ± 0.42	NS	NS	1.97 ± 0.49	NS	NS	1.95 ± 0.55
Endocardium	1.32 ± 0.12	0.05	0.87 ± 0.19	NS	NS	1.07 ± 0.12	NS	NS	1.71 ± 0.30	NS	NS	1.95 ± 0.51	NS	NS	1.99 ± 0.55	NS	NS	1.76 ± 0.48
Mean transmural	1.27 ± 0.19	0.05	0.74 ± 0.17	0.05	NS	0.89 ± 0.17	NS	0.04	1.71 ± 0.45	NS	NS	1.57 ± 0.33	NS	NS	1.83 ± 0.48	NS	NS	1.82 ± 0.47
Endo/epi ratio	1.38 ± 0.12	NS	1.50 ± 0.16	NS	NS	1.73 ± 0.25	NS	NS	1.38 ± 0.28	NS	NS	1.33 ± 0.19	NS	NS	1.07 ± 0.16	NS	NS	1.12 ± 0.16
N	11		11			6			5			6			5			6

Left ventricular anterior wall transmural blood flow values at temperatures between 37° C and 15° C are represented. After initial empty beating (control) determinations, hearts remained asystolic for subsequent data collections. Data are as follows: epicardial, outer myocardial, inner myocardial, and endocardial blood flow as well as mean transmural flow values. Endocardial/epicardial ratios are included for comparison. Myocardial blood flow = ml/min/gram of left ventricle.

p represents comparisons between specific interventions and p* compares each intervention to control levels. Statistical significance, $p < 0.05$. NS: not significant. Data are mean ± standard error of the mean.

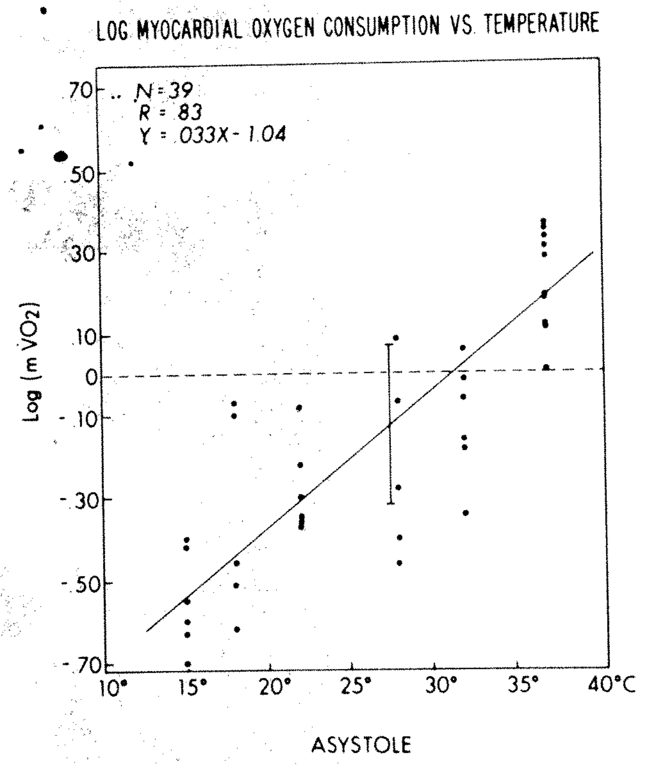


FIG. 5. For 11 dogs the logarithm of myocardial oxygen consumption is compared by linear regression analysis with temperatures between 37° and 15°C.

gen consumption in our experiments declined by 65% and became 1.85 ± 0.20 ml O_2/min/g. Similarly, McKeever and Gregg found that potassium arrest decreased oxygen requirements from approximately 7.7 ml O_2/min/100 g in working hearts to 2 ml O_2/min/100 g following brief arrest.[28] However, those preparations were not on cardiopulmonary bypass, and asystole was maintained only for a few seconds.

The minute oxygen consumption of depolarized ventricles in our study (1.85 ± 0.2 ml O_2/min/100 g) represents the basal requirement needed for cellular maintenance at 37°. Other experiments using isolated hearts have shown comparable reductions in MVO_2 with potassium induced normothermic asystole.[21,26] Recently, Buckberg determined that beta blockade, combined with pharmacologic arrest, using acetylcholine and potassium, decreased myocardial oxygen consumption at 37° from 5.59 to 1.1 ml O_2/min/100 g or by approximately 80%.[9] This reduction was somewhat greater than asystolic hearts presented and may reflect the responsiveness of basal metabolic mechanisms to adrenergic withdrawal even in the noncontracting heart.

In the experiments reported in this study with progressive cooling of asystolic ventricles to 32° an additional 55% decrement in oxygen expenditure oc-

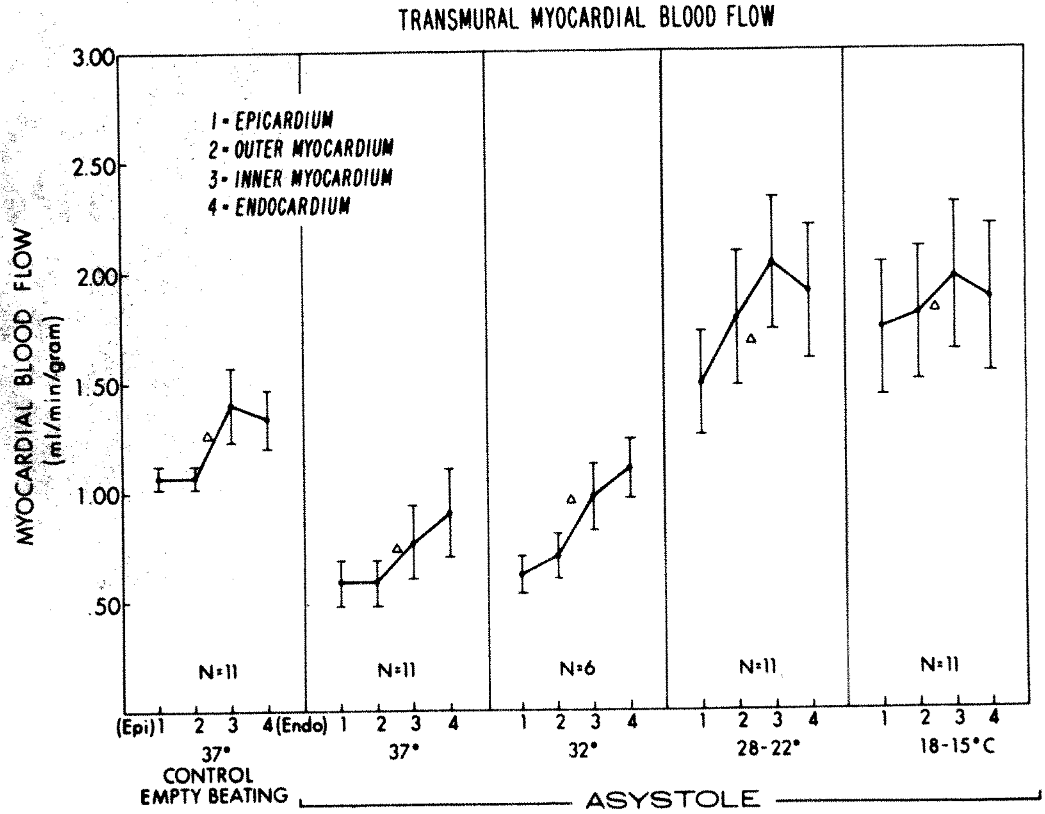


FIG. 6. Transmural myocardial blood flow (ml/min/g left ventricle) is represented for anterior papillary region in 11 dogs during ventricular cooling (37° to 15°C). No flow difference existed between this ventricular section and other myocardial regions. Hematocrit, 25 volumes %; Δ, mean transmural blood flow.

temperatures (28–15°) coronary arterial resistance decreased in the presence of a constant perfusion pressure. These vasodilatory effects of hypothermia are shown in Figure 10 and have been attributed to direct coronary interaction rather than reflex dilation.[12] The resulting generalized flow augmentation was distributed evenly to all ventricular layers, eventuating in homogeneous transmural cooling (±1°).[10]

One may surmise that perfused hearts with elevated blood flow should satisfy adequately energetic requirements present at lower temperatures. However, specific unphysiologic parameters tend to impede cellular oxygen delivery. Oxygen binds more firmly to human hemoglobin under hypothermic conditions.[3,33] Recent experiments by LePannas et al. have shown that dog blood has a p50 of 10.5 mmHg at 15° and, therefore, binds oxygen about 2.3 times tighter than at 37° (Fig. 11).[25] Additionally, Krogh demonstrated that tissue gaseous diffusion is impaired noticeably at lower temperatures.[15,23] Despite these factors, sufficient dissolved plasma oxygen should be present at 15° to satisfy demands measured in these arrested hearts. At present, there is no indication that these ventricles were unable to use available oxygen, and therefore, increased coronary blood flow does not appear to have resulted from hypoxic vasodilation.

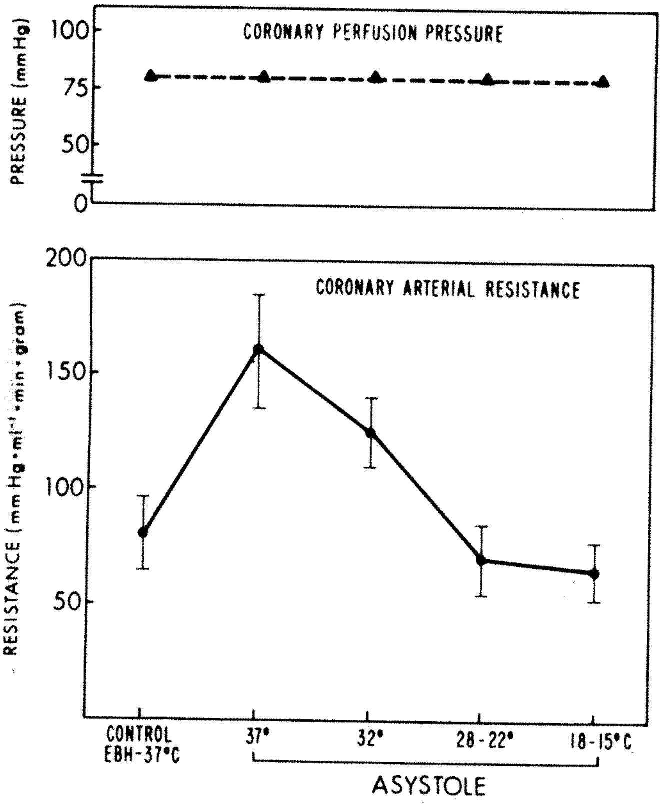


FIG. 10. Coronary arterial resistance decreased with progressive cooling while perfusion pressure was maintained at 80 mm Hg. This resulted in the generalized flow increment accompanying hypothermia. EBH, empty beating heart.

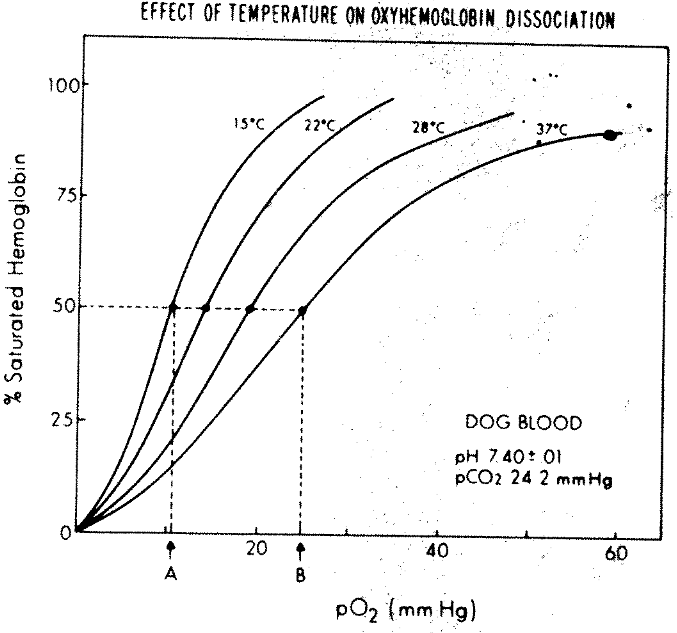


FIG. 11. Oxyhemoglobin dissociation curves for dog blood at temperatures between 37° and 15°. A, p50 at 15°; 10.5 mmHg.; B, p50 at 35° = 24.5 mmHg.

These studies confirm earlier reports suggesting that a sequential decrement in myocardial oxygen consumption occurs at lower temperatures independently of changes in heart rhythm. Removal of electromechanical activity alone does not decrease cellular oxygen demands maximally, and adjunctive hypothermia is still necessary to achieve the greatest energy conservation. During perfusion hypothermia, coronary autoregulation becomes markedly impaired, and flow paradoxically increases while metabolic requirements are minimal. However, it is not certain if tissue overperfusion occurring during suspended autoregulation is ultimately detrimental. Foremost, in pharmacologically arrested hearts with continuing coronary inflow, a significant oxygen demand still persists even after cooling to 15°. Because this meticulous attention must be paid to effective cooling to obtain maximal cardiac preservation, this is important for hearts undergoing cardiopulmonary bypass that may have limited functional reserve, especially during periods of induced ischemia.

Acknowledgments

Technical assistance was provided by Edward L. Ristaino, B.S. Recognition is given to the following for their assistance: Mrs. Maureen Evans Marino and Mrs. Lynn Zane for secretarial expertise; Mr.

Don Powell and Medical Media Productions of the Durham Veterans Administration Medical Center for excellent illustrations; Mr. Gary Pellom, Dr. Timothy Harward, and Dr. Bruce Wilhelmsen; Mr. Richard Steele for Van Slyke oxygen analysis; Dr. Herbert Saltzman for superb advice and use of the F. G. Hall Environmental Laboratory facilities; Dr. George LePannas and Joseph L. Bonnaventura for collaboration on oxyhemoglobin dissociation curves.

References

1. Adams, P. X., Cunningham, J. N., Jr., Trehan, N. K., et al.: Clinical Experience Using Potassium-induced Cardioplegia with Hypothermia in Aortic Valve Replacement. J. Thorac. Cardiovasc. Surg., 75:564, 1978.
2. Archie, J. P., Kirklin, J. W.: Effect of Hypothermic Perfusion on Myocardial Oxygen Consumption and Coronary Resistance. Surg. Forum, 24:186, 1973.
3. Astrup, P., Engel, K., Severinghaus, J. W., et al.: The Influence of Temperature and pH on the Dissociation Curve of Oxyhemoglobin of Human Blood. Scand. J. Clin. Lab Invest., 17:515, 1965.
4. Badeer, H.: Effect of Hypothermia on Oxygen Consumption and Energy Utilization of Heart. Circ. Res., 4:523, 1956.
5. Barcroft, J. and Dixon, W. E.: The Gaseous Metabolism of the Mammalian Heart. Part I. J. Physiol., (London) 35:182, 1906–07.
6. Bonnabeau, R. C., Sterns, L. P. and Lillehei, C. W.: Coronary Artery Resistance During Prolonged Profound Selective Hypothermia Under Cardiopulmonary Bypass. Trans. Amer. Soc. Artif. Int. Organs, 10:43, 1964.
7. Brantigan, J. W., Perna, A. M., Gardner, T. J., et al. Intramyocardial Gas Tensions in the Canine Heart During Anoxic Cardiac Arrest. Surg. Gynecol. Obstet. 134:67, 1972.
8. Braunwald, E.: Control of Myocardial Oxygen Consumption: Physiologic and Clinical Considerations. Am. J. Cardiol., 27:416, 1971.
9. Buckberg, G. D., Brazier, J. R., Nelson, R. L., et al.: Studies of the Effects of Hypothermia on Regional Myocardial Blood Flow and Metabolism During Cardiopulmonary bypass I. The Adequately Perfused Beating, Fibrillating, and Arrested Heart. J. Thorac. Cardiovasc. Surg., 73:87, 1977.
10. Chitwood, W. R., Jr., Hill, R. C., Kleinman, L. H., et al.: Pressure-flow Characteristics of the Coronary Collateral Circulation During Cardiopulmonary Bypass: Effects of Hypothermic Perfusion. Surg. Forum, 28:268, 1977.
11. Clerbaux, T., Gerets, G., Frans, A.: Oxygen Content Determination Using a New Analyzer: The Lex-O_2-Con. J. Lab Clin. Med., 82:342, 1973.
12. Cruickshank, E. W. H. and Subba Rau, A.: Reactions of Isolated Systemic and Coronary Arteries. J. Physiol., 64:65, 1927.
13. Fuhrman, G. J., Fuhrman, F. A. and Field, J. II: Metabolism of Rat Heart Slices, with Special Reference to Effects of Temperature and Anoxia. Am. J. Physiol., 163:642, 1950.
14. Gerola, A., Feinberg, H. and Katz, L. N.: Myocardial Oxygen Consumption and Coronary blood Flow in Hypothermia. Am. J. Physiol., 196:719, 1959.
15. Gibbs, C. L.: Cardiac Energetics. Physiol. Rev., 58:174, 1978.
16. Gott, V. L., Bartlett, M., Johnson, J. A., et al.: High Energy Phosphate Levels in the Human Heart During Potassium Citrate Arrest and Selective Hypothermic Arrest. Surg. Forum, 10:544, 1959.
17. Gott, V. L., Bartlett, M., Long, D. M., et al.: Myocardial Energy Substances in the Dog Heart During Potassium and Hypothermic Arrest. J. Appl. Physiol., 17:815, 1962.
18. Hardin, R. A., Scott, J. B. and Haddy, F. J.: Effects of Cardiac Cooling on Coronary Vascular Resistance in Normothermic Dogs. Am. J. Physiol., 199:163, 1960.
19. Jennings, R. B., Ganote, C. E.: Structural Changes in Myocardium During Acute Ischemia. Circ. Res., 34,35 (Suppl III):III–156, 1974.
20. Jennings, R. B., Hawkins, H. K., Lowe, J. E., et al.: Relation Between High Energy Phosphate and Lethal Injury in Myocardial Ischemia in the Dog. Am. J. Pathol., 92:187, 1978.
21. Jordan, J. and Lochner, W.: Über den anaeroben und aeroben Stöffwechsel des stillgestellten, küstlich perfundierten Warmbluterherzens. (On the Anerobic and Aerobic Metabolism of the Arrested, Artificially Perfused Mammalian Heart) Pfluegers Arch., 275:164, 1962.
22. Kent, B. and Pierce, E. C.: Oxygen Consumption During Cardiopulmonary Bypass in the Uniformly Cooled Dog. J. Appl. Physiol., 37:917, 1974.
23. Krogh, A.: The Anatomy and Physiology of Capillaries. Yale Univ. Press, New Haven, 1929, p. 267.
24. Kübler, W. and Spieckermann, P. G.: Regulation of Glycolysis in the Ischemic and the Anoxic Myocardium. J. Mol. Cell Cardiol., 1:351, 1970.
25. LePannas, G., Chitwood, W. R., Jr., Bonnaventura, J., et al.: unpublished data, 1978.
26. Lochner, W., Arnold, G. and Muller-Ruckholtz, E. R.: Metabolism of the Artificially Arrested Heart and of the Gas-Perfused Heart. Am. J. Cardiol., 22:299, 1968.
27. McConnell, D. H., Brazier, J. R., Cooper, N., et al.: Studies of the Effects of Hypothermia on Regional Myocardial Blood flow and Metabolism During Cardiopulmonary Bypass. II. Ischemia During Moderate Hypothermia in Continually Perfused Beating Hearts. J. Thorac. Cardiovasc. Surg., 73:95, 1977.
28. McKeever, W. P., Gregg, D. E. and Canney, P. C.: Oxygen Uptake of the Nonworking Left Ventricle. Circ. Res. 6:612, 1958.
29. Miller, D. W., Hessel, E. A., Winterschied, L. C., et al.: Current Practice of Coronary Artery Bypass Surgery: Results of a National Survey. J. Thorac. Cardiovasc. Surg., 73:75, 1977.
30. Monroe, R. G., Strang, R. H., LaFarge, C. G., et al.: Ventricular Performance, Pressure-volume Relationships, and O_2 Consumption During Hypothermia. Am. J. Physiol., 206:67, 1964.
31. Olinger, G. N. and Boncheck, L. I.: Ventricular Venting During Coronary Revascularization: Assessment of Benefit by Intraoperative Ventricular Function Curves. Ann. Thorac. Surg., 26:535, 1978.
32. Roughton, F. J. W.: Transport of Oxygen and Carbon Dioxide. *In* Handbook of Physiology: Respiration. American Physiological Society, Washington, D.C., 1964, Vol. 1, Ch. 31, pp 776–777.
33. Rudolph, A. M. and Heymann, M. A.: The Circulation of the Fetus in Utero. Methods for Studying Distribution of Blood Flow, Cardiac Output and Organ Blood Flow. Circ. Res., 21:163, 1967.
34. Van Slyke, D. D. and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement. J. Biol. Chem., 61:523, 1924.
35. Valeri, C. R., Zaroulis, C. G., Marchionni, L., et al.: A Simple Method for Measuring Oxygen Content in Blood. J. Lab Clin. Med., 79:1035, 1972.
36. Wright, R. N., Levitsky, S., Holland, C., et al. Beneficial Effects of Potassium Cardioplegia During Intermittent Aortic Cross-Clamping and Reperfusion. J. Surg. Res., 24:201, 1978.
37. Skeleton, L. C. and Sonnenblick, E. H.: Myocardial Energetics. *In* Cardiac Mechanics: Physiological, Clinical and Mathematical Considerations, Mirsky, I., et al. (eds.). John Wiley and Sons, New York, 1969, pp 113–137.
38. Tyers, G. F. O., William, E. H. and Hughes, H. C.: Effect of Perfusate Temperature on Myocardial Protection from Ischemia. J. Thoracic. Cardiovasc. Surg., 73:766, 1977.

Influence of Increasing Carbohydrate Intake on Glucose Kinetics in Injured Patients

DAVID H. ELWYN, PH.D., JOHN M. KINNEY, M.D. MALAYAPPA JEEVANANDAM, PH.D.,
FRANK E. GUMP, M.D., JOHN R. BROELL, M.S.

The metabolic and hormonal effect of glucose loads, ranging from 125 to 504 g/70 kg/day, were studied in severely injured patients. There was little or no correlation of glucose intake with nitrogen balance, plasma glucose, fatty acid concentrations, or epinephrine excretion. Increased norepinephrine excretion correlated with and may have resulted from increased glucose intake. Serum glucagon concentrations averaged 320 pg/ml and were not depressed by glucose intake. Insulin concentrations rose with glucose intake but were low for the level of plasma glucose. Glucose oxidation and non-oxidative metabolism, including glycogen deposition, correlated well with glucose intake. Gluconeogenesis from alanine was much higher than normal but was completely suppressed at very high intakes. The data imply that cycling of glucose, with glycerol, glycogen, or both, increased with increasing glucose intake.

THE PRIMARY SOURCE of calories in parenteral nutrition continues to be glucose. The ability to provide nutritional support for the severely injured patient is dependent upon the body's capacity to handle high glucose loads. The growing utilization of total parenteral nutrition (TPN) has now been extended by some to the immediate postinjury or postoperative period. The abnormal glucose metabolism that marks the early "flow" stage is therefore of increasing clinical interest.

This early flow stage after injury may be characterized as one in which a superabundant supply of nutrients is provided solely from body stores.[37] High levels of glucose are available which are needed and used by healing wounds.[42] Increased breakdown of muscle protein makes amino acids available for synthesis of visceral and blood proteins and for gluconeogenesis. Increased fat mobilization provides an adequate supply of fatty acids for those tissues which do not specifically require glucose. This state differs from fasting in that glucose concentrations are high, there is little or no ketosis, particularly in severe injury,[34] protein catabolism is much greater, and resting energy expenditure is above rather than below normal. These metabolic changes are associated with an hormonal pattern that includes abnormally high levels of catecholamines, glucagon, and glucocorticoids, and insulin levels that are low in light of the high glucose concentrations. Both the endocrine and metabolic changes appear to derive in large part from increased sympathetic activity.[37]

From the Department of Surgery and Institute of Human Nutrition, College of Physicians and Surgeons of Columbia University, New York, New York

One feature of this state is that the normal effects of high glucose concentrations are attenuated or absent. Plasma fatty acid concentrations, which are markedly lowered by high glucose intakes in the normal state,[8,41] remain high. Gluconeogenesis, which is normally suppressed in the presence of high glucose concentration, persists in the traumatized or septic patient.[11,22] It seems reasonable to expect that this "glucose resistance," observed in the untreated patient or during infusion of 5% glucose solutions, would continue to express itself during higher rates of glucose administration.

The present study was undertaken to explore the effects of increasing glucose intakes to levels that are utilized for providing conventional TPN. Glucose kinetics were studied in severely injured patients. In addition, associated hormonal and substrate changes were determined in an effort to better identify the metabolic abnormalities responsible for glucose resistance in these patients.

Materials and Methods

Subjects

Nine men with severe accidental injuries were studied; one (HM) was infected; the others were not.

Reprint requests: David H. Elwyn, Ph.D. Department of Surgery, College of Physicians and Surgeons, 630 West 168th Street, New York, New York 10032

Submitted for publication: October 10, 1978.

0003-4932/79/0700/0117 $01.05 © J. B. Lippincott Company

TABLE 1. *Diagnosis, Degree of Trauma, Age, and Time of Study for 9 Men with Accidental Injuries*

Patient	Age	Height (cm)	Weight (kg)	Surface area (m^2)	Diagnosis	Degree of Trauma on Scale of 10	Start of Study (Days After Injury or Infection)
PR	24	180	104	2.14	Auto accident; fracture of right femur and pelvis, blunt abdominal trauma	9	13
RV	34	167	79	1.88	Gun shot, head and abdomen	8	6
HW	28	191	74	2.00	Gun shot, abdomen; left nephrectomy	8	1
VV	30	168	71	1.72	Gun shot, abdomen	7	3
AJ	36	175	82	1.99	Multiple stab wounds, abdomen	6	2
AC	47	178	76	1.90	Multiple contusions, pelvic fracture	6	3
HM	21	163	61	1.66	Infection of crush wound, right leg, with invasive sepsis	7	6
WC	56	170	85	1.96	Fracture of pelvis, left hip, femur and tibia (open)	9	2
BL	26	173	79	1.91	Multiple long bone fractures	8	7

All were physically healthy prior to the accident. In all but one case, studies were started within one week of the accident or onset of infection (Table 1). Five patients had multiple fractures, the others had extensive soft tissue damage. The severity of trauma, on the average was estimated to be 7.5 on a scale of 10. None of the subjects, with minor exceptions, were able to take oral nourishment. All were bedridden during the study. The details of this study and possible risks and benefits were discussed with each patient, members of his family, and his physician. Written consent was obtained in all cases.

Study Protocol

Eight patients were given continuous infusions of glucose at a constant rate for four days. In five instances 10% dextrose was infused peripherally without amino acid or vitamin supplements. In three patients, in whom a central catheter was already inserted for other purposes, total parenteral nutrition, including amino acids and vitamins, was provided. Fluid and electrolyte intakes were adjusted to individual requirements. Nitrogen and energy balances were measured during all four days. Blood samples were drawn daily at 08:00 for determination of serum insulin and glucagon, plasma glucose, free fatty acids (FFA), and blood urea nitrogen (BUN). U-^{14}C-alanine (20–30 μc.) was injected as a single bolus on the second day, and U-^{14}C-glucose (15–20 μc.) also as a single bolus, was injected on the third day. Ten blood samples were drawn just prior to, and at 5, 15, 30, 45, 60, 90, 120, 180, and 300 minutes after each injection for determination of the concentration and specific activity of blood glucose. The total amount and specific activity of expired CO_2 was measured at frequent intervals up to 12 hours after each injection.

One subject, HW, was maintained at two different levels of glucose intake, each for 3 days. On the third day of each period he was given an injection of glucose; no alanine was given.

Analyses

Balance measurements. All intake, whether oral or infused, was measured by differences in weights of the full and emptied containers. The amounts of each constituent (H_2O, N, etc.) were calculated from the manufacturer's specifications or by direct analysis in this laboratory according to established procedures.[2] Energy contents of diets were calculated from published values and, in the case of oral intake, were corrected for digestibility.[26] Urine, feces, and drainage were collected daily and analyzed for N, H_2O, Na^+ and K^+ content. In addition urea was determined in urine and drainage, creatinine was determined in urine, and glucose was determined in those urine samples in which qualitative tests (Ketodiastix®*) were positive. A manual, micro-Kjeldahl procedure was used for digesting samples for total N determination. Subsequent analysis of total N, and analyses of urea, creatinine, Na^+ and K^+ were carried out with single channel automated analyzers according to the manufacturer's procedures.†

Gas exchange. Oxygen consumption and CO_2 production were measured using a rigid lucite head canopy developed in this laboratory.[18,36] This permits frequent measurements of relatively long duration, three to five periods per day of 40–60 minutes each, with minimal discomfort to the patient.

Blood determinations. Plasma glucose was determined by an automated glucose oxidase procedure.‡ Blood urea nitrogen was measured by the clinical chemistry laboratory. Plasma FFA concentrations were determined by the procedure of Dole and Meinertz.[4] Plasma insulin was measured by radioimmunoassay using Pharmacia kits. Glucagon measurements were kindly performed in the laboratory of Dr. J. B. Price, of this institution, using antiserums and methods supplied by Dr. Roger H. Unger, of the University of Texas Health Sciences Center, Dallas, Texas. Radioactivity in plasma glucose was measured by conversion to potassium gluconate,[21] recrystallization, and counting in a liquid scintillation counter.§ Urinary epinephrine and norepinephrine were measured by the trihydroxyindole method as adapted by Viktora et al.[39] with minor modifications.

---

* Ames Company, Elkhart, Indiana.

† Auto Analyzer, Technicon Company, Tarrytown, New York.

‡ Glucose Analyzer, Beckman Instruments, Inc., Fullerton, California.

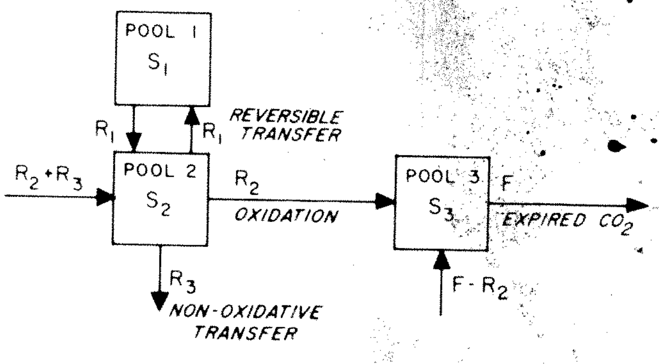


FIG. 1. Three-pool model of glucose metabolism. For explanation see text. Adapted from Long et al.[23]

Calculations

Glucose-^{14}C model. The method for calculating rates of glucose metabolism based on ^{14}C-glucose has been described in detail elsewhere[35] and will only be summarized here. The method involves injection of a single bolus of glucose U-^{14}C and repeated measurements, over the ensuing 6–12 hours, of the specific activity of blood glucose and the amount and radioactivity of expired CO_2. A computer model, schematized in Figure 1, is fitted to the data to derive the best values for three rates and the size of the glucose and CO_2 pools (S_2 and S_3). The rate of CO_2 production (rate F in Fig. 1) is measured directly. The physiologic significance of these rates may be explained with references to the simplified metabolic scheme shown in Figure 2. The rate R_1 (Fig. 1) refers to the rate of interchange of glucose with compounds, represented by pool 1 (Fig. 1), which return isotope to the glucose pool. The most important of these are glycogen, glycerol, and pyruvate and its derivatives, such as lactate and alanine. This corresponds to, but is not a quantitative measure of, glucose recycling. It is determined with poor precision by this method. The main function of R_1 in this model is to permit more accurate measurement of rates R_2 and R_3; the rate R_1, as measured here, has little or no physiologic significance.

Rate R_2 represents the rate of glucose oxidation and is equal to the sum of the contributions of glucose to the rates r_a, r_b, and r_c in Figure 2. Rate R_3 represents the rate of conversion of glucose to compounds from which there is negligible return of isotope and which, therefore, during the course of the experiment retain the isotope. This represents, essentially, the sum of the rates of conversion of glucose to glycogen, protein,

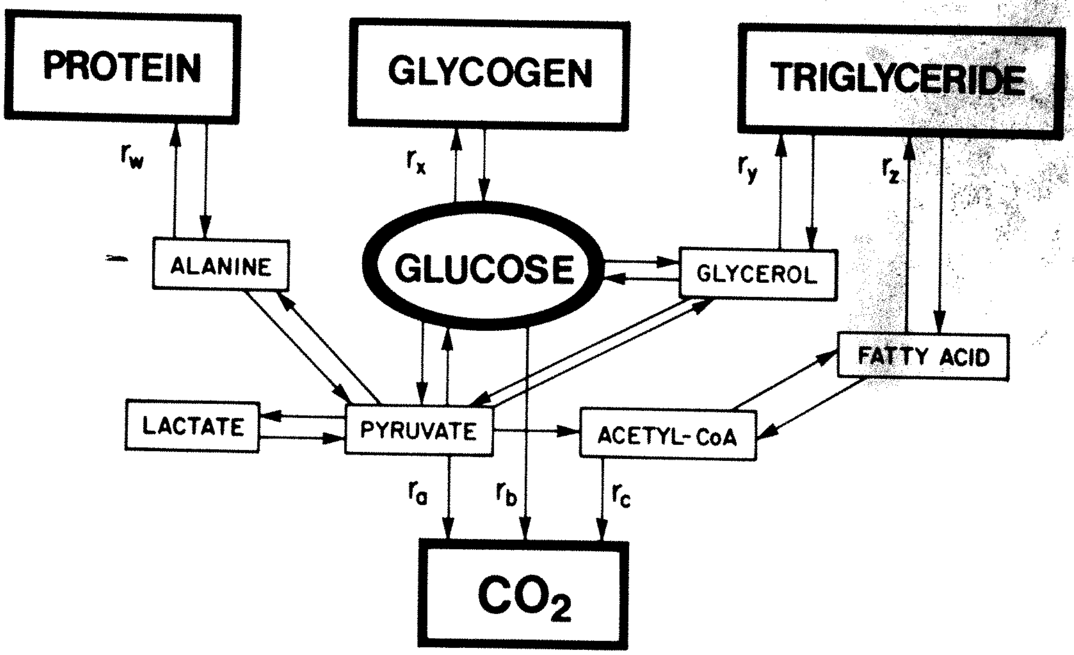


FIG. 2. Simplified scheme of glucose metabolism.

---

§ Amersham-Searle.

TABLE 2. *Metabolic Characteristics of Traumatized Patients*

	Mean*	SEM	Range
Energy intake (kcal/70 kg/day)	1258		496 to 2060
Nonprotein respiratory quotient (mole/mole)	0.86		0.79 to 1
Glucose intake (g/70 kg/day)	312		125 to 504
Resting energy expenditure (% of predicted)	118	6.6	91 to 159
Nitrogen balance (g/m²/day)	−7.3	0.67	−4 to −9.7
Plasma glucose (mg/dl)	152	10	115 to 216
Plasma free fatty acids (mmole/l)	0.57	0.11	0.18 to 1.14
Serum insulin (μU/ml)	34	10	10 to 103
Serum glucagon (pg/ml)	324	142	47 to 1286
Insulin/glucagon ration (mole/mole)	4.2	1.3	0.7 to 12
Urinary norepinephrine (μg/day/70 kg)	297	76	15 to 682
Urinary epinephrine (μg/day/70 kg)	54	10	22 to 82
Glucose oxidation† (g/70 kg/day)			
Measured by indirect calorimetry	231	33	114 to 403
Measured with ^{14}C-glucose	250	31	133 to 468
Nonoxidative glucose metabolism† (g/70 kg/day), measured with ^{14}C-glucose	252	40	98 to 479
Total glucose turnover† (g/70 kg/day), measured with ^{14}C-glucose	502	70	221 to 947
Glucose balance† (g/70 kg/day), measured by indirect calorimetry	120	21	14 to 197
Alanine to glucose‡ (% dose ^{14}C)	10.4	2.6	1.9 to 21.4

* Mean daily values for 9 subjects each studied for 4–6 days.
† Day of glucose injection only.
‡ Day of alanine injection only.

and triglycerides, and corresponds to the contribution of glucose to rates r_w, r_x, r_y and r_z in Figure 2. Although the rates of conversion of glucose to other intermediates may be quite rapid, they are taken into account either as part of recycling (rate R_1) or as intermediates in the pathways to CO_2, protein and triglycerides (rates R_2 and R_3). Rate R_3 is referred to as the rate of nonoxidative glucose metabolism. The sum of R_2 and R_3 is taken as total glucose turnover, which by this definition does not include the Cori cycle or other recycling included in rate R_1. Rates R_2 and R_3, as measured here, are unidirectional rather than net rates. Since there is negligible conversion of CO_2 to glucose, the unidirectional rate R_2 is equal to net oxidation of glucose. By contrast, synthesis of glucose from unlabeled glycogen, protein, and fat is quantitatively significant, and can be greater than the reverse reactions. Therefore R_3 is strictly a unidirectional rate and this model does not measure net conversion of glucose to fat, protein, or glycogen, either singly or as their sum.

The accuracy of rates R_2 and R_3 depends on the assumption that the specific activity of glucose is the same, when measured in blood, as at the sites of reaction in various tissues. Since the glucose pool is largely extracellular, this appears to be a reasonable assumption.

Glucose oxidation and balance by indirect calorimetry. Calculation of resting energy expenditure and of the rates of glucose oxidation from measurements of N excretion, O_2 consumption, and CO_2 production was carried out by traditional methods of indirect calorimetry.[38] This method measures the net rate of glucose oxidation, which should be equal to that measured by the glucose ^{14}C model if the assumptions of both methods are valid.

Glucose balance is taken to be the difference between glucose intake and glucose expenditure as measured, at rest, by indirect calorimetry. Since in these experiments there was no *net* conversion of glucose to fat (nonprotein RQ $\leq$ 1), glucose expenditure was equal to glucose oxidation. Glucose balance is then equal to glycogen balance less any additional expenditure of glucose, during physical activity, over and above that measured at rest. Since, in this study, the patients were completely confined to bed, glucose balance may be presumed to approximate glycogen balance.

Conversion of alanine to glucose. The conversion of alanine to glucose is expressed as the percentage of the administered dose found in glucose when the specific activity of plasma glucose was at a maximum.[22] It is calculated by multiplying the maximum plasma glucose specific activity by the size of the glucose pool as measured with labeled glucose. Unlike the rates calculated from the glucose model and indirect calorimetry, this provides only a semiquantitative index of the rate of conversion of alanine to glucose. Intracellular concentrations of alanine are much higher than those in blood. The specific activities of amino acids differ markedly between blood and various tissues. In addition, the ratios of specific activities in tissues and blood vary under different conditions.[5,9] It seems unlikely, therefore, that more elaborate models or measurement of the specific activity of alanine in blood would significantly improve on the method used here.

Results

The metabolic characteristics of these patients (Table 2) indicate that they were severely traumatized, in agreement with the clinical estimates (Table 1). An increase of 18% above predicted values for resting energy expenditure is in the range previously observed for multiple long bone fractures.[16] Nitrogen balance of −7.3 g/m² was markedly negative, compared to

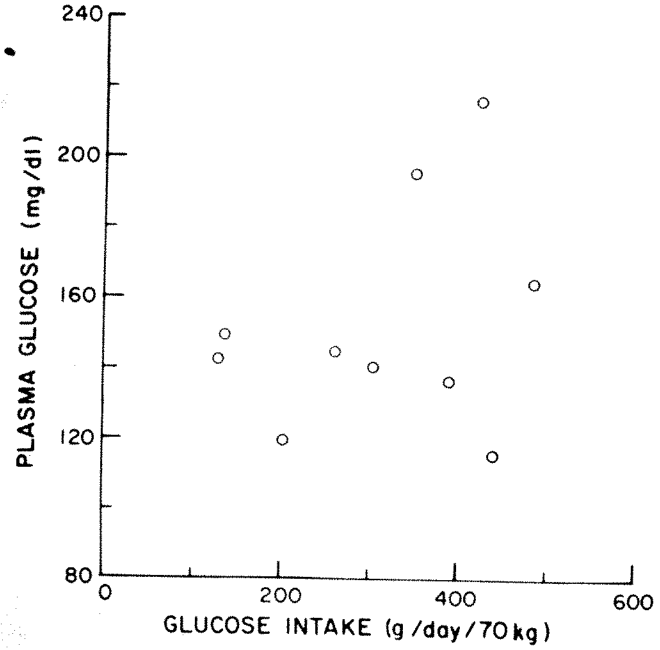


FIG. 3. Effect of glucose intake on plasma glucose concentation in injured patients.

values of 0 to −3 for normal young men on similar intravenous diets.[45] Serum insulin concentrations were in the range of normal subjects receiving equal rates of glucose infusions,[45] but were abnormally low with respect to plasma glucose concentrations. Free fatty acids were in a normal postabsorptive range, but were higher than normal for the levels of glucose intake and concentration.[8,41,45] Urinary excretion of norepinephrine and epinephrine averaged seven and four times normal values (43 ± 20 and 14 ± 11 mg/day/70 kg respectively, as determined in our laboratory). Serum glucagon concentrations averaged 324 pg/ml, very much higher than values of 11–66 pg/ml observed in normal young men on similar glucose intakes.[45]

Metabolic Responses to Increasing Glucose Intake

Daily glucose intake (Table 2) ranged widely, from 125 g, provided by the customary administration of 5% dextrose, to 500 g/day, almost enough to meet resting energy expenditure. A number of the measured metabolic parameters correlated well with glucose intake, others did not. Plasma concentrations of glucose (Fig. 3) and FFA (Fig. 4), and N balance (Fig. 5) showed little correlation, when compared to glucose intake, as shown by slopes which did not differ significantly from zero, and small correlation coefficients (Table 3).

Serum insulin was positively correlated with glucose intake with a slope significantly above zero (Table 3, Fig. 6).

Serum pancreatic glucagon, somewhat surprisingly,

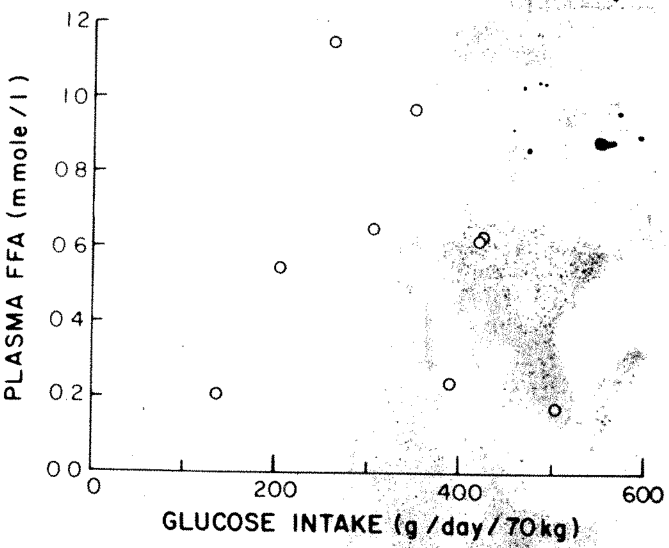


FIG. 4. Effect of glucose intake on plasma free fatty acid concentration in injured patients.

increased with increasing glucose intake (Table 3, Fig. 7). Although this increase was not significantly different from zero (Table 3), it nevertheless suggests that there was no marked decrease in glucagon concentrations with increasing glucose intake, as occurs

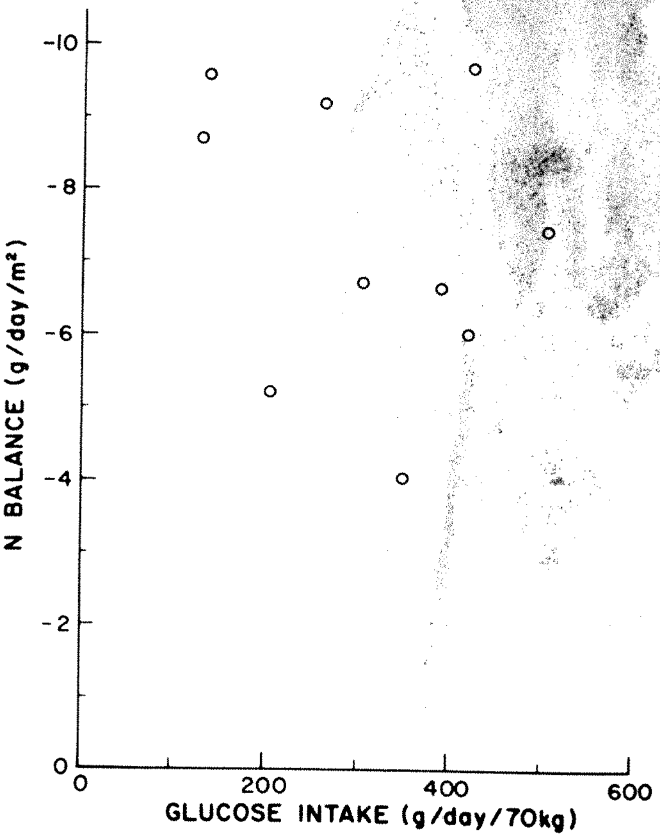


FIG. 5. Effect of glucose intake on nitrogen balance in injured patients.

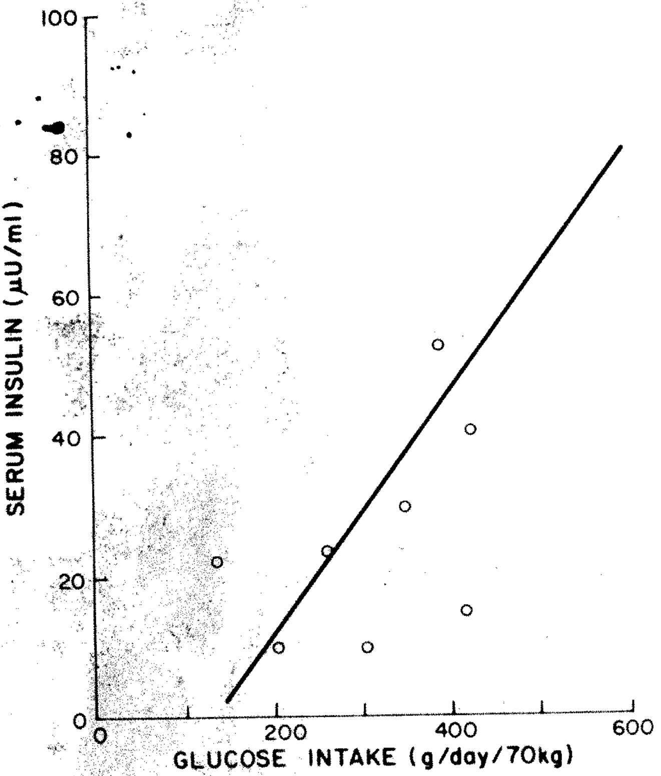


FIG. 6. Effect of glucose intake on serum insulin concentration in injured patients. Slope = 0.17 ± 0.07 (SEM).

in the normal individual.[45] The resulting insulin: glucagon rations were very low (Table 2) for the amounts of glucose infused and showed no significant change with glucose intake (Table 3).

Urinary norepinephrine showed a statistically significant increase with increasing glucose intake as shown for all nine patients in Figure 8 and Table 3. When the data on the three patients who were given amino acids were omitted, the correlation between glucose intake and norepinephrine excretion improved as indicated by a correlation coefficient of 0.9. One patient was given two levels of glucose intake, 129 and 356 g/day/70 kg, for 3 days each. Mean values for norepinephrine excretion were 15 μg/day/70 kg on the low intake and 82 μg on the high intake.

TABLE 3. *Correlation of Various Metabolic Parameters with the Rate of Glucose Intake**

	Slope	95% Confidence Limits of Slope	r
Plasma glucose	0.083	−0.083 to 0.166	0.33
Plasma FFA	−0.0004	−0.0026 to 0.0018	−0.13
Nitrogen balance	0.003	−0.007 to 0.013	0.22
Serum insulin	0.17	0.03 to 0.31	0.67
Serum pancreatic glucagon	1.4	−1 to 3.8	0.41
Insulin/glucagon ratio	0.007	−0.017 to 0.024	0.24
Urinary norepinephrine	1.2	0 to 2.3	0.6
Urinary epinephrine	0.02	−0.18 to 0.12	0.1
Glucose oxidation	0.54	0.32 to 0.76	0.86
Nonoxidative glucose metabolism	0.75	0.54 to 0.96	0.93
Total glucose turnover	1.29	0.88 to 1.70	0.91
Glucose balance	0.37	0.23 to 0.51	0.88
^{14}C-Alanine to glucose	−0.036	−0.057 to −0.015	0.82

* Units as given in Table 2.

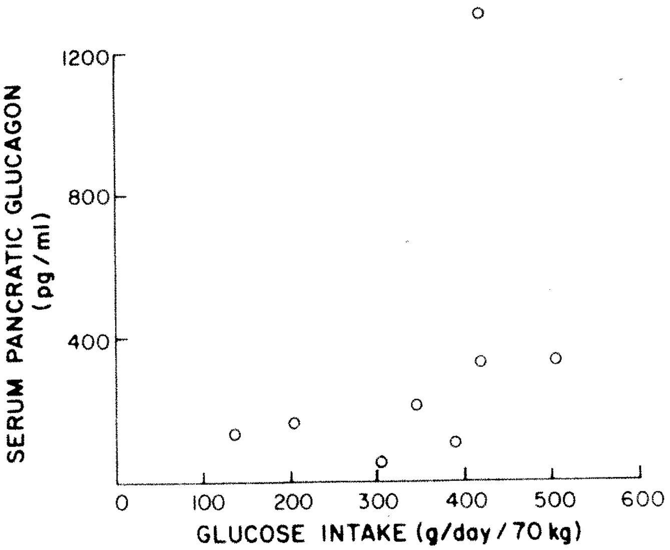


FIG. 7. Effect of glucose intake on serum concentration of pancreatic glucagon.

Epinephrine excretion showed no correlation with glucose intake (Table 3).

Glucose metabolism as measured with ^{14}C. Glucose oxidation and non-oxidative glucose metabolism, as

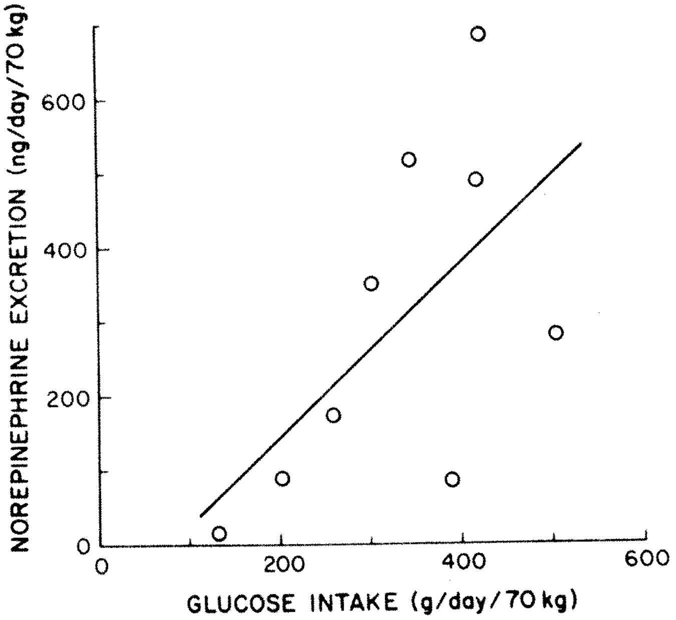


FIG. 8. Effect of glucose intake on daily norepinephrine excretion. Slope = 1.2 ± 0.6 (SEM).

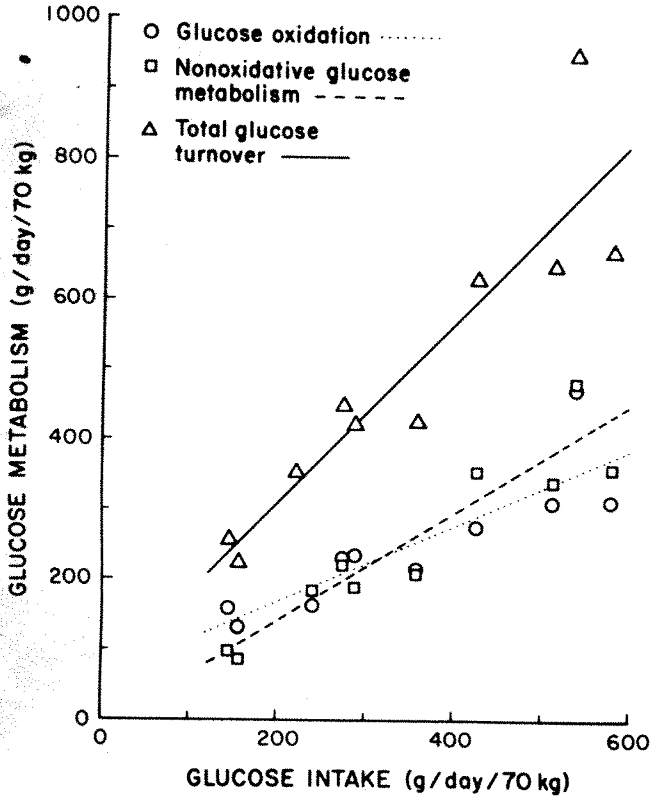


FIG. 9. Effect of glucose intake on glucose oxidation, nonoxidative glucose metabolism, and their sum, total glucose turnover, as measured by means of ^{14}C glucose. The slopes of the regression lines are 0.54 for glucose oxidation, 0.75 for nonoxidative glucose metabolism, and 1.29 for their sum.

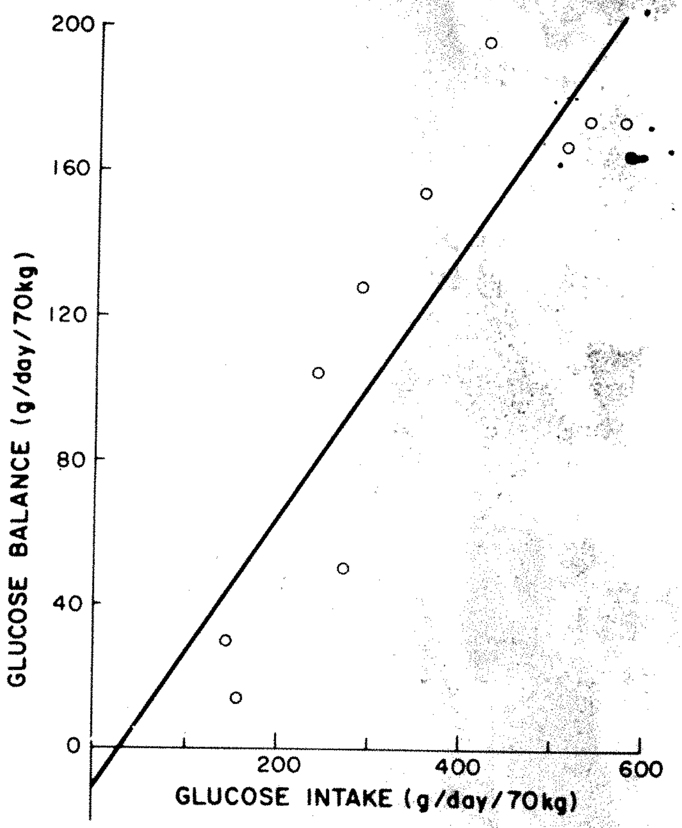


FIG. 10. Effect of glucose intake on glucose balance in injured patients. Slope = 0.37 ± 0.07 (SEM).

estimated with labeled glucose, both showed excellent correlation with glucose intake (Table 3, Fig. 9). Oxidative and nonoxidative metabolism were roughly equal to each other over the entire range of glucose intake. Total glucose turnover, the sum of oxidative and nonoxidative reactions, appeared to be somewhat higher (30–50%) than glucose intake over the entire range of intake.

Glucose balance measured by indirect calorimetry. Glucose balance correlated well with intake (Table 3, Fig. 10). It was positive in all instances and accounted for about one-third of intake, approximately 60 g at an intake of 200 g, and of 200 g at an intake of 600 g (Fig. 10). A positive glucose balance, as measured at rest, consists of two main components: (1) deposition of glycogen and (2) increased expenditure of glucose, above resting values, during physical activity. Since the patients in this study were confined to bed at all times, the major part of the observed positive glucose balance was probably due to glycogen deposition.

Comparison of glucose model and indirect calorimetry. The fraction of total CO_2 derived from glucose oxidation calculated from the ^{14}C-glucose model is compared in Figure 11 to that calculated by indirect

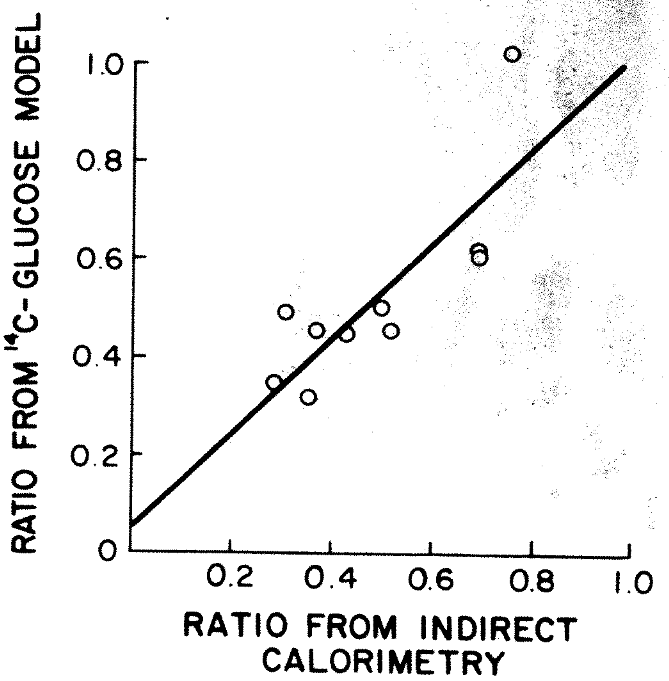


FIG. 11. Comparison of glucose oxidation in injured patients, expressed as a ratio to total CO_2 production, measured simultaneously by two different methods: (1) by injection of ^{14}C glucose; and (2) by indirect calorimetry. Slope = 0.95 ± 0.27 (SEM).

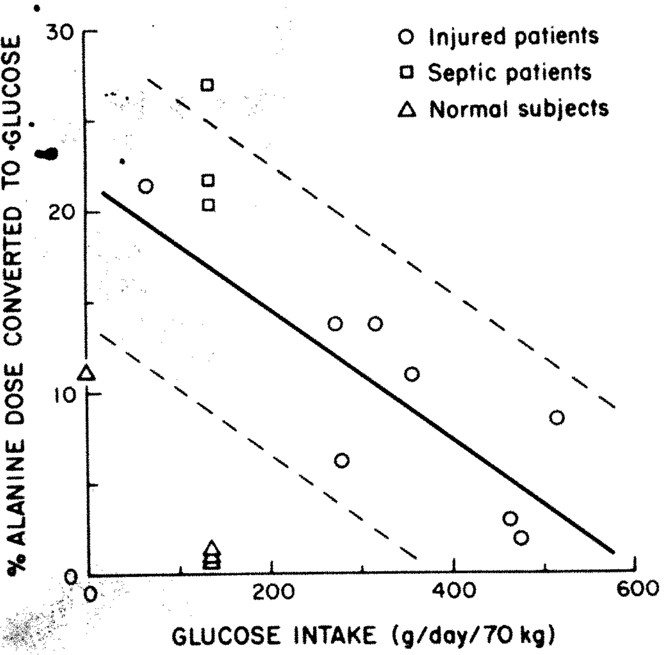


FIG. 12. Effect of glucose on gluconeogenesis in injured patients. Gluconeogenesis was measured as the percentage of alanine incorporation into glucose at the time of maximum glucose specific activity. The regression line and 95% confidence limits (*dotted lines*) are based solely on the data for the injured patients from the present study and do not include the septic patients or normal subjects, data for whom are taken from Long et al.[22] Slope = − 0.036 ± 0.11 (SEM).

calorimetry on the same day. There is good agreement between the two methods as shown by a slope of 0.95 ± 0.27 (theoretical = 1) and a correlation coefficient of 0.82.

Conversion of alanine to glucose. The percentage of the dose of ^{14}C-alanine converted to glucose showed an inverse linear correlation with glucose intake for the injured patients in this study (Table 3, Fig. 12). Values for three septic patients and four normal subjects from Long et al.[22] are also shown. It is clear that the injured and septic patients constitute a separate group from the normal subjects. Increasing glucose intake suppresses the conversion of alanine to glucose in both groups. However, zero conversion is reached at an intake of about 150 g/day in the normal and 600 g/day in the injured subjects.

Discussion

Hormonal Response to Glucose

These studies of traumatized patients indicate quite different reponses to hypocaloric glucose administration from those seen in normal subjects. Of particular significance are the rise in norepinephrine excretion and the lack of a decrease in glucagon concentration with increasing glucose intake. However, the finding that norepinephrine excretion is positively correlated with glucose intake does not necessarily mean that increased glucose intake is the cause of the increase in norepinephrine. An alternate explanation could be that the sicker patients were given greater amounts of glucose and that the amount of urinary catecholamines reflected only the severity of trauma. The purpose of the present experiment was primarily exploratory, to identify the significant metabolic and endocrine changes associated with increasing intakes of glucose. In eight patients, only a single level of glucose was given, and in general, the design of the study was not such as to provide definitive proof of one or another of these possible explanations. Nevertheless, there is suggestive evidence of a causal relation between glucose intake and norepinephrine excretion. There was no correlation (r = 0.03) between glucose intake and clinical estimates of the severity of trauma (Table 1). The patient studied at two different levels of glucose intake excreted more norepinephrine at the higher intake. Three additional trauma patients (studied by Y.A. Carpentier in this laboratory), given two different levels of glucose intake, also excreted more norepinephrine at the higher intake than at the lower intake. We may conclude, then, that it is quite likely that, in these patients representing the early "flow" stage of trauma, increasing glucose intake causes an increase in norepinephrine excretion. This is consistent with findings, in the rat, that increased dietary intake results in increased norepinephrine turnover and excretion.[19]

Catecholamines stimulate glucagon secretion and inhibit insulin production.[31] The high serum glucagon values in the present study, which were not suppressed by glucose infusion, can be at least partially explained by the high levels of norepinephrine. Likewise the low values for insulin, in consideration of the high plasma glucose concentrations, may be in large part due to inhibition of insulin release by norepinephrine.

Effect of Glucose Intake on Glucose Metabolism

There was, not surprisingly, a very close correlation between rates of glucose intake and glucose metabolism. This was true not only for glucose oxidation but also for non-oxidative glucose metabolism. These data are consistent with previous findings[11,22–24] that the hyperglycemia of trauma and sepsis is associated with increased glucose production rather than reduced glucose utilization.

The good agreement in estimating rates of glucose oxidation between indirect calorimetry and the glucose model, served to validate the assumptions of the latter method, and in particular the assumption that the specific activity of blood glucose is a valid measure of that of the glucose pool. This assumption is of major importance in calculating both oxidative and non-oxidative rates of glucose metabolism. Therefore, the agreement between methods tends also to validate estimates of the rate of non-oxidative metabolism of glucose.

Gluconeogenesis

The conversion of alanine to glucose in injured patients was much greater than normal at a low glucose intake. Nevertheless, it was completely suppressed at high glucose intakes and the amount converted appears to be a linear function of the rate of glucose intake. In contrast, the rate of oxidation of alanine, as measured by appearance of radioactivity in expired CO_2, appears to be relatively constant, at about 30% of the dose, and to be independent of glucose intake or pathologic state.[22] Also there was little difference in specific activity of plasma alanine between normal and injured subjects.[22] Since pyruvate is an obligatory intermediate in conversion of alanine to both glucose and CO_2, these data suggest that inhibition of glucose synthesis is occurring between pyruvate and glucose rather than between alanine and pyruvate. This is in keeping with much evidence from other sources[6,28] that an important, if not the important, site of regulation of gluconeogenesis from pyruvate involves the enzyme phosphoenolpyruvate carboxykinase, which catalyzes the conversion of oxalacetate to phosphoenolpyruvate (PEP). These considerations suggest that incorporation of isotope from alanine into glucose serves as a semi-quantitative index of the rate of glucogenesis, not just from alanine, but from all sources which must first be converted to PEP. These include all other glucogenic amino acids, as well as lactate.

Thus, the data presented here indicate that, in trauma, gluconeogenesis from both protein and lactate persists at abnormally high levels in the face of high rates of glucose intake. Nevertheless, at very high intakes (600 g/day) it is completely suppressed. The observed hormonal pattern is consistent with this. High and relatively unchanging values for glucagon should oppose inhibition, whereas insulin levels, which increase proportionately with glucose intake, are eventually high enough to overcome the glucagon effect and serve to suppress gluconeogenesis.

Total glucose turnover, as noted above, was more than 30% greater than glucose intake at all levels of intake (Fig. 9). This finding indicates that the unidirectional synthesis of glucose increased rather than decreased with increasing glucose intake. The isotopic alanine data, however, indicates complete suppression of gluconeogenesis from lactate and protein at high glucose intakes. This implies that there is increased unidirectional synthesis of glucose from other sources. The only two sources of quantitative significance are glycogen and glycerol. In the case of glycogen, as discussed more fully below, there was a marked increase in net glycogen deposition with increased glucose intake. It is possible that, simultaneously, there was a large increase in the unidirectional rates of glycogen synthesis and breakdown, leading to a high rate of interchange of isotopic glucose from the glucose pool with nonisotopic glucose from glycogen stores. There was no net conversion of glucose to fat in these studies, as indicated by nonprotein respiratory quotients, which never exceeded 1, and therefore no net conversion of glucose to glycerol. Nevertheless, there could have been an increase in the rate of triglyceride turnover in adipose tissue that would utilize labeled glucose to provide glycerolphosphate for triglyceride synthesis and release unlabeled glycerol, which would be resynthesized into glucose in the liver.

Thus, the finding of increased glucose turnover with decreased gluconeogenesis from alanine, implies that, in trauma, glucose administration causes an increased turnover of glycogen, triglycerides, or both. We would not expect to find such increases in normal subjects under glucose loading, although to our knowledge such studies have not been carried out.

Glycogen Deposition

The net rate of glycogen deposition, measured as glucose balance on the third day of glucose infusion, was approximately one-third the rate of glucose intake and reached values of more than 150 g/day/70 kg in some patients (Fig. 10). These rates seem very high when it is considered that: (1) the extreme range of diet-induced changes in glycogen storage in normal subjects can be calculated from data of Hultman et al.[12,13] to be about 400 g/70 kg; (2) that dietary intake was equal to or less than resting energy expenditure; and (3) that depleted patients on high carbohydrate diets have much lower rates of glycogen deposition (less than 50 g/day/70 kg) by the third day of a new dietary regimen than do these traumatized patients. Thus in these trauma patients there appears to be an abnormally high rate of glycogen deposition at all levels of glucose intake. This occurs despite very high concentrations of both norepinephrine and glucagon, which would be expected to stimulate breakdown of glycogen in both muscle and liver.

The effects of increasing glucose intake on glucose metabolism in trauma patients may be summarized as follows:

(1) Plasma glucose concentrations are maintained at

the already high level associated with trauma but are not significantly increased.

(2) Rates of glucose oxidation and non-oxidative metabolism increase proportionately with intake.

(3) There is an abnormally high rate of glycogen deposition which is proportional to glucose intake.

(4) Gluconeogenesis from protein is abnormally high but can be completely suppressed with an intake of approximately 600 g glucose per day.

(5) Glucose recycling with glycogen, glycerol, or both is increased with increasing intake.

Pathophysiologic Significance of Glucose Loads in Injured Patients

The patients in this study present a metabolic and hormonal pattern that is characteristic of the early flow phase of the response to severe injury.[1,17,37] This pattern includes increased resting energy expenditure, increased N excretion, hyperglycemia with increased glucose turnover, and increased fatty acid and glycerol turnover.[7,40] Elevated glucagon concentrations have been reported in burns[30,33,44] and in injury.[10,25,32] Increased plasma concentrations of catecholamines were seen in accidental trauma.[14] Increased urinary excretion of catecholamines was associated with high glucagon levels in burns.[43,44] Although not measured in this study, serum glucocorticoids are also elevated in trauma.[1] The characteristic pattern of glucose metabolism in trauma may be simulated in normal subjects by infusion of glucagon, cortisol, and epinephrine together, in amounts sufficient to raise serum concentration to levels seen in injured patients.* Since no two of these hormones can produce this effect, this suggests that a minimum condition for the metabolic response to trauma is increased production of all three of these hormones.

In a teleologic sense, this metabolic pattern may be viewed as a mobilization of the body's own stores of protein, fat and carbohydrate to provide normal or above normal levels of circulating substrates, glucose, FFA, and amino acids, without requiring any dietary intake. Thus gluconeogenesis is maintained despite high plasma glucose concentrations, and is able to meet normal requirements of the brain and other tissues as well as the increased requirements for glucose demonstrated for wound tissue.[42] Increased levels of amino acids are available for synthesis of viscera and blood proteins. High levels of fatty acid can meet the energy needs of heart and skeletal muscle sparing glucose for those tissues which specifically require it. In some respects this pattern is similar to that seen in fasting or acute starvation in normal subjects in whom there is also a dependence on the body's own stores of nutrients.[20] This includes increased plasma levels of glucagon and cortisol, increased excretion†[15] and plasma levels[3] of catecholamines, increased mobilization of protein, fat, and carbohydrate stores, and increased gluconeogenesis. However, there are differences between the two catabolic states. Trauma patients tend to be hyperglycemic, whereas fasted subjects become hypoglycmeic; ketosis develops rapidly in fasting normal subjects but is frequently absent in injured patients.[34]

The present studies indicate that the response to glucose loading is very different in the injured patient than in the normal fasted subjects. Infusion of glucose for 3–4 days after fasting resulted in a fall in glucagon concentrations and a decrease in catecholamine excretion to normal values.† In injured patients, by contrast, glucagon concentrations remained high (Fig. 7, Table 3) and catecholamine excretion was increased (Fig. 8, Table 3). It required much greater loads of glucose to suppress gluconeogenesis from protein in injured patients (Fig. 12) than in fasted subjects. Recycling of glucose with glycogen or glycerol is increased in injury. Nitrogen excretion is markedly reduced by giving glucose to fasted subjects†[27,29,45] but showed little change in the injured patients (Fig. 5).

These differences in response to glucose loading are consistent with the distinct etiologies of these two catabolic states. The abnormal metabolic pattern in fasting is of dietary origin and can be markedly affected or returned to normal by dietary means. The metabolic pattern in trauma appears to be highly resistant to dietary intervention, at least in the early phases of the flow stage as studied here. This raises, once again, the question as to the extent one should expect to correct the hypercatabolism of injury by dietary means. The term "nutritional stress" has been placed on inadequate nutrient intake in surgical patients. The present study indicates that providing carbohydrate may not always decrease this stress but in some conditions may add to it.

Acknowledgement

We are grateful to Oliver E. Owen, George A. Reichard and Douglas W. Wilmore for helpful comments during preparation of this manuscript.

References

1. Alberti, K. G. M. M., Batson, G. F. and Johnston, D. G.: Hormonal changes in trauma: Role of Cortisol. *In* Richards J. R. and Kinney J. M., (eds.) Nutritional Aspects of Care in the Critically Ill. Edinburgh, Churchill Livingston, 1977, p 225.

---

* Personal communication from Robert S. Sherwin, Department of Medicine, Yale University, New Haven, Connecticut.

† Unpublished observation from this laboratory.

2. Association of Official Agriculture Chemists. Official Methods of Analysis, 9th ed. Washington D. C., 1963.
3. Christensen, N. J.: Plasma Norepinephrine and Epinephrine in Untreated Diabetics, During Fasting and After Insulin Administration. Diabetes 23:1, 1974.
4. Dole, V. P. and Meinertz, H.: Microdetermination of Long Chain Fatty Acids in Plasma and Tissues. J. Biol. Chem. 235:2595, 1960.
5. Elwyn, D. H.: The role of the liver in the regulation of amino acid and protein metabolism. *In* Munro, H. N., (ed.) Mammalian Protein Metabolism., Vol. IV. New York, Academic Press, 1970.
6. Exton, J. H.: Gluconeogenesis. Metabolism, 21:945, 1972.
7. Fleck, A.: The early metabolic response to injury. *In* Ledingham, I., (ed.) Shock. Amsterdam, Excerpta Medica, 1976, p. 77.
8. Fritz, I. B.: Factors Influencing the Rates of Long Chain Fatty Acid Oxidation and Synthesis in Mammalian Systems. Physiol. Rev. 41:52, 1961.
9. Gan, J. G. and Jeffay, H.: Origins and Metabolism of the Intracellular Amino Acid Pools in the Rat. Biochim. Biophys. Acta, 148:448, 1967.
10. Giddings, A. E. B., O'Connor, K. J., Rowlands, B. J., et al.: The Relationship of Plasma Glucagon to the Hyperglycaemia and Hyperinsulinaemia of Surgical Operation. Br. J. Surg., 63:612, 1976.
11. Gump, F. E., Long, C. L., Killian, P., et al.: Studies of Glucose Intolerance in Septic Injured Patients. J. Trauma, 14:378, 1974.
12. Hultman, E., Bergstrom, J. and Roch-Norlund, A. E.: Glycogen Storage in Human Skeletal Muscle. *In* Pernow, B., Saltin, B., (eds.) Muscle Metabolism During Exercise. New York, Plenum Press, 1971, p. 273.
13. Hultman, E., Nilsson, L. H.: Liver glycogen in man. Effect of different diets and muscular exercise. *In* Pernow, B., Saltin, B., (eds.) Muscle Metabolism During Exercise. New York, Plenum Press, 1971, p. 143.
14. Jaattela, A., Allko, A., Avikainen, V., et al. Plasma Catecholamines in Severely Injured Patients: a Prospective Study on 45 Patients with Multiple Injuries. Br. J. Surg., 62:177, 1975.
15. Januszewicz, W., Sznajderman-Ciswicka, M. and Wocical B.: Urinary Excretion of Catecholamines in Fasting Obese Subjects. J. Clin. Endocrinol. Metab., 27:130, 1967.
16. Kinney, J. M.: Calorie–Nitrogen: Disease and injury relationships. *In* White, P. L. and Nagy, M. (eds) *Total Parenteral Nutrition*. Acton, Massachusetts, Publishing Science Group, 1974.
17. Kinney, J. M.: The metabolic response to injury. *In* Richards, J. R. and Kinney, J. M., (eds.) Nutritional Aspects of Care in the Critically Ill. Edinburgh, Churchill Livingston, 1977, p. 95.
18. Kinney, J. M., Morgan, A. P., Dominguez, F. J., et al.: A Method for Continuous Measurement of Gas Exchange and Expired Radioactivity in Acutely Ill Patients. Metabolism, 13:205, 1964.
19. Landsberg, L. and Young, J. B.: Fasting, Feeding and Regulation of the Sympathetic Nervous System. N. Engl. J. Med., 298:1295, 1978.
20. Levenson, S.: Starvation. *In* Richards, J. R., and Kinney, J. M., (eds.) Nutritional Aspects of Care in the Critically Ill. Edinburgh, Churchill Livingston, 1977, p. 3.
21. Long, C. L. and Geiger, J. W.: Liquid Scintillation Counting of the Potassium Gluconate Derivative of Blood Glucose. Anal. Biochem., 10:253, 1965.
22. Long, C. L., Kinney, J. M. and Geiger, J. M.: Nonsuppressability of Gluconeogenesis by Glucose in Septic Patients. Metabolism, 25:193, 1976.
23. Long, C. L., Spencer, J. L., Kinney, J. M., et al.: Carbohydrate Metabolism in Normal Man and Effect of Glucose Infusion. J. Appl. Physiol., 31:102, 1971.
24. Long, C. L., Spencer, J. L., Kinney, J. M., et al.: Carbohydrate Metabolism in Man: Effect of Elective Operations and Major Injury. J. Appl. Physiol., 31:110, 1971.
25. Meguid, M. M., Brennan, M. F., Aoki, T. T. et al.: Hormone-substrate Interrelationships Following Trauma. Arch. Surg., 109:776, 1974.
26. Merrill, A. L. and Watt, B. K.: Energy Value of Foods. Agriculture Handbook No. 74, Washington, D.C., U.S. Govt. Printing Office. March 1955.
27. Munro, H. N.: Regulation of protein metabolism. *In* Munro, H. N. and Allison, J. B., (eds.) Mammalian Protein Metabolism, Vol. I. New York, Academic Press, 1964, p 381.
28. Newsholme, E. A. and Start, C.: Regulation in Metabolism. New York, John Wiley, 1973.
29. O'Connell, R. C., Morgan, A. P., Aoki, T. T., et al.: Nitrogen Conservation in Starvation: Graded Responses to Intravenous Glucose. J. Clin. Endocrinol. Metab., 39:555, 1974.
30. Orton, I. C., Segal, A. W., Bloom, S. R. et al.: Hypersecretion of Glucagon and Gastrin in Severely Burnt Patients. Br. Med. J., 2:170, 1975.
31. Porte, D. Jr. and Robertson, R. P.: Control of Insulin Secretion by Catecholamines, Stress, and the Sympathetic Nervous System. Fed. Proc., 32:1792, 1973.
32. Russell, R. C. G., Walker, C. J. and Bloom, S. R.: Hyperglucogonaemia in the Surgical Patient. Br. Med. J., 1:10, 1974.
33. Schuck, L. W., Eaton, P. R. and Shuck, J. M.: Glucagon, Insulin and Glucose Relationships in the Severely Burned Patients. Surg. Forum., 26:39, 1975.
34. Smith, R., Fuller, D. J., Wedge, J. H., et al.: Initial Effect of Injury on Ketone Bodies and Other Blood Metabolites. Lancet, 1:1, 1975.
35. Spencer, J. L., Long, C. L. and Kinney, J. M.: A Mathematical Model for Glucose Metabolism in Man. Ind. Eng. Chem., 10: 1, 1971.
36. Spencer, J. L., Zikria, A. B., Kinney, J. M., et al.: A System for the Continuous Measurement of Gas Exchange and Respiratory Functions. J. Appl. Physiol., 33:523, 1972.
37. Stoner, H. B.: An integrated neuro-endocrine response to injury. *In* Wilkinson, A. W. and Cuthbertson, D. (eds.) Metabolism and the Response to Injury. Tunbridge Wells: Pittman, 1976, p 194.
38. Swift, R. W. and French, C. F.: Energy Metabolism and Nutrition. Washington, D.C., The Scarecrow Press, 1954.
39. Viktora, J. F., Baukal, A. and Wolff, F. W.: New Automated Fluorometric Method for Estimation of Small Amounts of Adrenaline and Noradrenaline. Anal. Biochem., 23:513, 1968.
40. Warner, W. A.: Release of Fatty Acids Following Trauma. J. Trauma, 9:693, 1969.
41. Waterhouse, G., Baker, N. and Rostami, H.: Effects of Glucose Ingestion on the Metabolism of Free Fatty Acids in Human Subjects. J. Lipid. Res., 10:487, 1969.
42. Wilmore, D. W., Aulick, L. H., Mason, A. D. et al.: Influence of the Burn Wound on Local and Systemic Responses to Injury. Ann. Surg., 186:444, 1977.
43. Wilmore, D. W., Long, J. M., Mason, A. D., et al.: Catecholamines: Mediator of the Hypermetabolic Response to Thermal Injury. Ann. Surg. 180:653, 1974.
44. Wilmore, D. W., Moglan, J. A., Lindsey, C. A., et al.: Hyperglucagonemia Following Thermal Injury: Insulin and Glucagon in the Posttraumatic Catabolic State. Surg. Forum, 24:99, 1973.
45. Wolfe, B. M., Culebras, J. M., Sim, A. J. W., et al.: Substrate Interaction in Intravenous Feeding. Ann. Surg., 186:518, 1977.

Book Reviews

Disorders of the Gastrointestinal Tract, Disorders of the Liver, Nutritional Disorders. John M. Dietschy. 418 pp. New York, Grune and Stratton, Inc. 1976. $24.50.

THIS IS VOLUME I of a new textbook of medicine entitled "The Science and Practice of Clinical Medicine" with Jay P. Sanford as Editor-in-Chief. The editor of this first volume, John M. Dietschy, has obtained contributions from 56 authors, most of whom are recognized authorities in gastroenterology. Disorders of the entire gastrointestinal tract, pancreas, liver, biliary tract, diaphragm, peritoneum, mesentery, omentum as well as nutritional diseases are discussed. The major sections begin with a review of anatomy, normal physiology and biochemical functions of the gastrointestinal organ followed by a discussion of diagnostic procedures applicable to evaluating diseases of these organs. Specific diseases of each organ are then discussed. Appropriate references follow each subsection. The sections on physiology and differential diagnosis are the strong points. Occasional errors occur such as the diagram demonstrating the operation to treat postvagotomy diarrhea is a diagram of the remedial operation to correct the dumping syndrome.

A vast amount of material is covered in a concise manner. Because of the lack of in-depth discussion, this text may not interest the physician or surgeon specializing in diseases of the alimentary tract. However, the book may be recommended to students and physicians wishing to review recent practical information relative to the gastrointestinal tract.

JOHN L. SAWYERS, M.D.

Davis-Christopher Textbook of Surgery, (eleventh edition). David C. Sabiston (ed.). Philadelphia, W. B. Saunders Company. 1977.

THE ELEVENTH EDITION of the *Davis-Christopher Textbook of Surgery* has little resemblance to its early siblings. Dr. Sabiston and his two hundred contributors have produced a new volume that is encyclopedic in its scope and marks another milestone in the history of surgery.

The primary reaction of older readers will be a mixture of satisfaction because the book proves that a surgeon's knowledge is so extensive, and of despair because each individual discovers so much that is unknown to him. On the other hand, primary emphasis throughout the volume is placed on the basic sciences upon which surgeons must build, and fortunately the book is dedicated to medical students and to residents who often are much more familiar with these considerations than their elders.

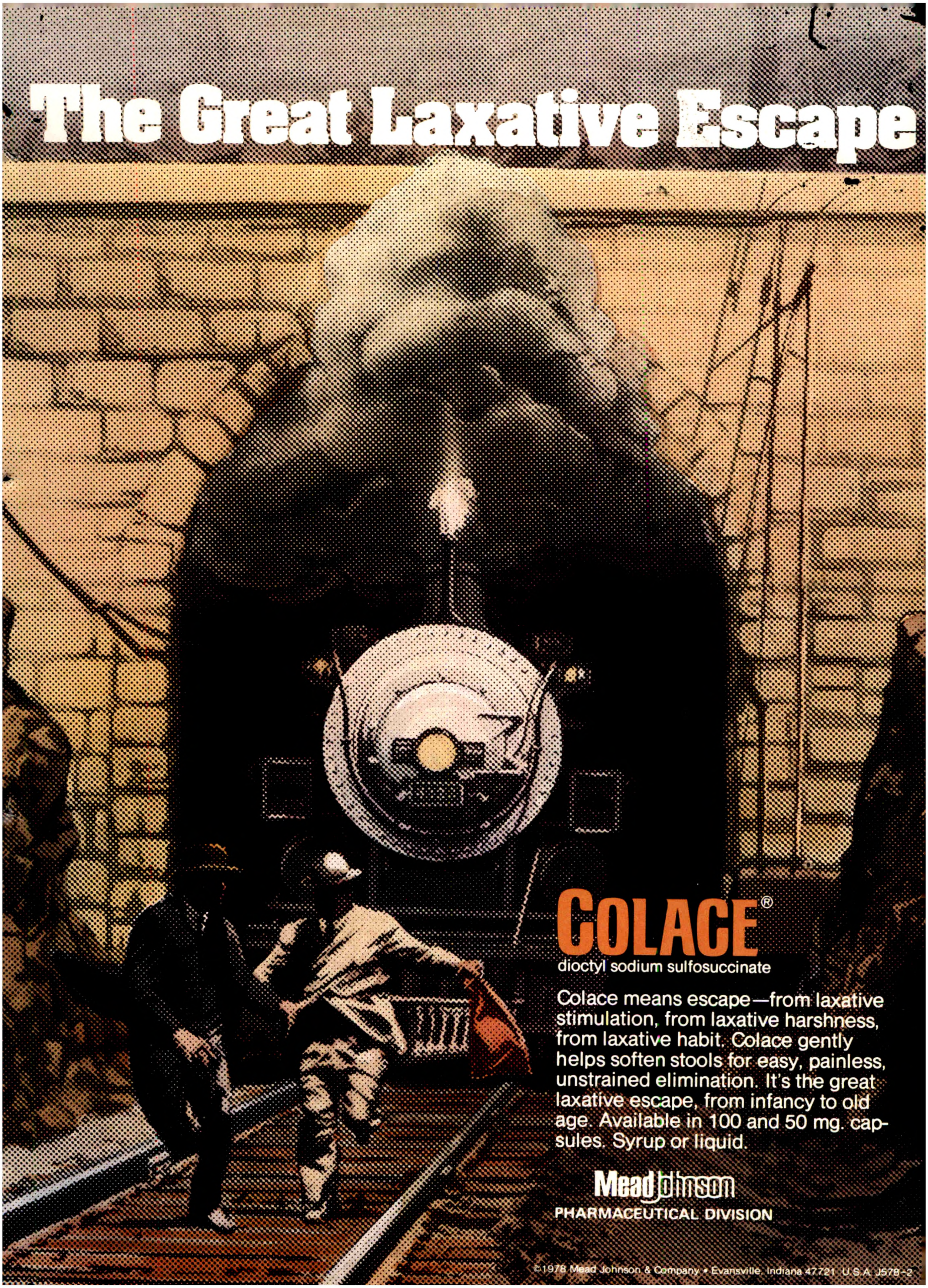
Approximately one-quarter of the book is devoted to general principles, or in the truest sense of the word, to general surgery. The chapters in these sections are of uniform excellence, all written by outstanding authorities. The remainder of the book is devoted to the specialties. Here the distribution and content tend to vary. For example, abdominal surgery is treated very thoroughly. Discussions of the heart and vascular systems are extraordinarily complete—possibly a reflection of the author's own primary interests. Pediatric surgery receives only brief attention, and plastic surgery no special distinction. Other features of the book that deserve commendation include the chapter on history of the frequent additional historical notes that introduce many of the chapters. Numerous illustrations enliven the text.

It is fascinating to compare the eleventh with the second edition that appeared 40 years ago. For example, at that time the answer to early cancer of the breast was clear; the present edition reflects a state of indecision. The roster of infections has changed completely. Antibiotics, vascular and cardiac surgery, and respiratory therapy were either unborn or in their infancy. Only future editions can determine what is progress and what is mere change.

A reviewer must make some criticisms, however trivial they may be. The first is that in common with all surgical texts the problems of pregnancy and delivery are considered only peripherally. Certainly nature's original transplant theoretically and practically deserves closer attention. A second is that some students may be completely overwhelmed by the magnitude of this work that emphasizes the reasons for surgical therapy rather than the technical details. How about a chapter describing some truly minor surgery that the student can see early in his career to build his ego? How about the lowly foot, for example, which receives scant attention?

But away with such trivial considerations that would tend to equate practical techniques with underlying biological mechanisms. This is truly a monumental book. However, a word to prospective customers is this: buy the two-volume edition if you plan to use it for bedtime reading.

CLAUDE E. WELCH, M.D.



The Great Laxative Escape

COLACE®

dioctyl sodium sulfosuccinate

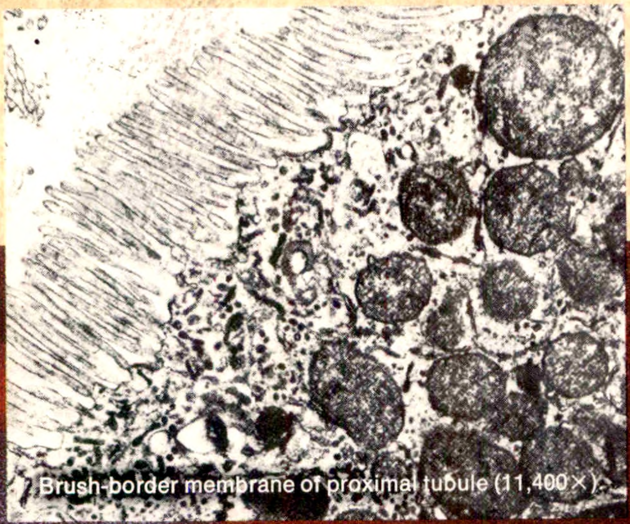
Colace means escape—from laxative stimulation, from laxative harshness, from laxative habit. Colace gently helps soften stools for easy, painless, unstrained elimination. It's the great laxative escape, from infancy to old age. Available in 100 and 50 mg. capsules. Syrup or liquid.

Mead Johnson

PHARMACEUTICAL DIVISION

©1978 Mead Johnson & Company • Evansville, Indiana 47721 U.S.A. J578-2

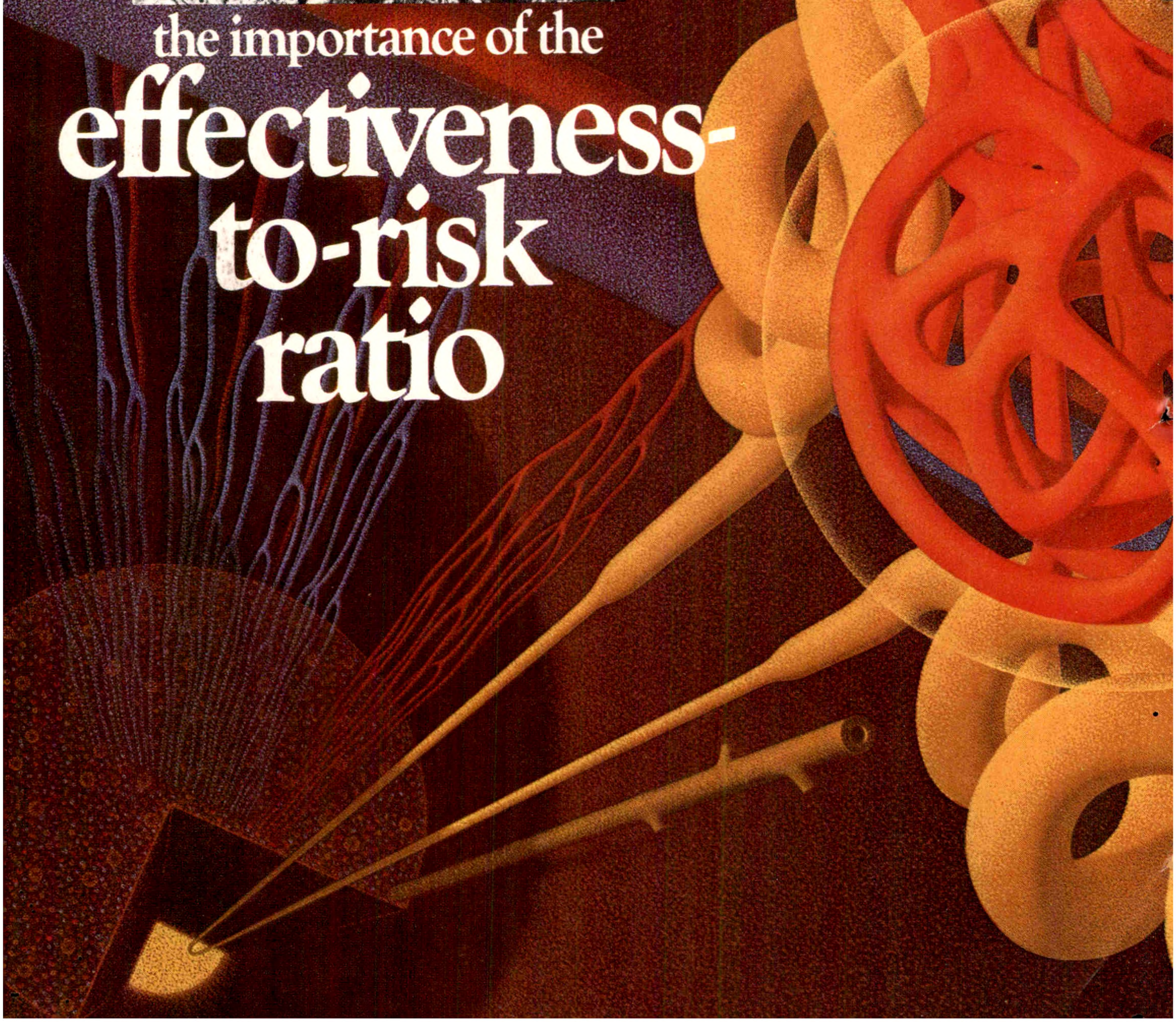
Selecting an aminoglycoside: the importance of the effectiveness-to-risk ratio



Brush-border membrane of proximal tubule (11,400×).

In patients with serious bacterial infection, the choice of antibiotic therapy is usually made on the basis of the effectiveness-to-risk ratio. This consideration is particularly important when an aminoglycoside antibiotic is indicated.

The activity of Nebcin® (tobramycin sulfate, Lilly) against a wide range of gram-negative organisms is now well known. A review of worldwide literature shows "that tobramycin has significant antibacterial activity and that it is the most potent of all aminoglycosides against *P. aeruginosa*. The antibacterial



activities of tobramycin and gentamicin against members of the Enterobacteriaceae are comparable, with each agent possessing slightly greater activity than the other against selected strains of any species."[1]

Nebcin is indicated in the treatment of

- septicemia
- serious lower respiratory infections
- gastrointestinal infections, including peritonitis
- serious complicated and recurrent urinary tract infections
- serious skin, bone, and soft-tissue infections, including burns

caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa, Escherichia coli, Proteus* sp. (indole-positive and indole-negative), *Providencia, Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

The proximal tubule

The proximal tubule is the site in the renal system where aminoglycosides produce nephrotoxicity.

An investigator has studied the urinary excretion of alanine aminopeptidase, a principal enzyme of the brush-border membrane of the proximal tubule.[2] Levels of the enzyme become elevated in the urine as a result of toxic lesions in acute tubular necrosis or of inflammatory processes in the kidney, such as rejection crisis. In measurements of the effect of aminoglycosides (administered for three consecutive days) on the excretion of this enzyme by healthy humans, tobramycin appeared to have a minimum effect on the brush-border membrane.

Another investigative team has studied the relationship between tissue concentration and toxicity.[3] The toxicity of aminoglycosides may be related to the degree of their binding to tissue. Hence, aminoglycosides that accumulate less may be less nephrotoxic.

All aminoglycosides are potentially nephrotoxic and ototoxic. Therefore, patients should be monitored closely when aminoglycosides are being used. Patients with impaired renal function, the elderly, those with underlying disease, those with prior exposure to potentially nephrotoxic agents, and those with poor host resistance are at special risk. During clinical trials in 3506 patients treated with tobramycin, investigators reported drug-related nephrotoxicity in 1.5 percent (53 patients).[4]

In view of the effectiveness of Nebcin and the relatively low risk of nephrotoxicity, tobramycin can be an appropriate choice for patients requiring aminoglycoside therapy.

References

1. J. Infect. Dis., *134* (Supplement):S3, 1976.
2. J. Antimicrob. Chemother., *4* (Supplement A):23, 1978.
3. J. Antimicrob. Chemother., *4* (Supplement A):53, 1978.
4. Med. J. Aust., *2* (Special Supplement):22, 1977.

tobramycin/Nebcin® ◆I.M./I.V.

tobramycin sulfate

80 mg* in 2-ml ampoules

*Equivalent to tobramycin.

Please see following page for a brief summary of the prescribing information.

800730

Nebcin® I.M./I.V.
tobramycin sulfate

Summary of Prescribing Information

> **WARNINGS**
>
> Patients treated with Nebcin should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.
>
> Both vestibular and auditory ototoxicity can occur. Eighth-nerve impairment may develop if patients have preexisting renal damage and if Nebcin is administered for longer periods or in higher doses than those recommended.
>
> Tobramycin is potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by cylindruria, oliguria, proteinuria, or evidence of nitrogen retention (increasing BUN, NPN, or creatinine). Evidence of impairment in renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.
>
> Nebcin should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.
>
> In the case of overdosage or toxic reactions, peritoneal dialysis or hemodialysis will help remove tobramycin from the blood.
>
> Serum concentrations should be monitored when feasible, and prolonged concentrations above 12 mcg/ml should be avoided. Urine should be examined for increased excretion of protein, cells, and casts.
>
> Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, and vancomycin, should be avoided.
>
> Nebcin should not be given concurrently with potent diuretics. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.
>
> *Usage in Pregnancy*—Safety of this product for use during pregnancy has not been established.

Description: Tobramycin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from the actinomycete *Streptomyces tenebrarius*. Nebcin Injection is a clear and colorless sterile aqueous solution for parenteral administration. It is stable and requires no refrigeration.

Indications and Usage: Nebcin is indicated for the treatment of serious infections caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa, Escherichia coli, Proteus* sp. (indole-positive and indole-negative), *Providencia, Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

Nebcin is indicated in the treatment of septicemia; central-nervous-system infections, including meningitis; neonatal sepsis; serious lower respiratory infections; gastrointestinal infections, including peritonitis; and serious skin, bone, and soft-tissue infections, including burns, caused by the susceptible organisms listed above. Clinical studies have shown Nebcin also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Nebcin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that the causative organisms are resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom gram-negative septicemia, neonatal sepsis, or meningitis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Nebcin may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the WARNINGS box above.

Contraindication: A history of hypersensitivity to tobramycin is a contraindication to its use.

Warnings: *See* WARNINGS box above.

Precautions: Specimens should be collected during therapy for examination, as recommended in the WARNINGS box.

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg/kg). The possibility that prolonged or secondary apnea may occur should be considered if tobramycin is administered to anesthetized patients who are also receiving neuromuscular blocking agents, such as succinylcholine or tubocurarine.

Cross-allergenicity among aminoglycosides has been demonstrated.

If overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

Adverse Reactions: *Nephrotoxicity*—Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, cylindruria, and increased proteinuria, have been reported, especially in patients with a history of renal impairment who are treated for longer periods or with higher doses than those recommended.

Neurotoxicity—Adverse effects on both the vestibular and auditory branches of the eighth nerve have been noted, especially in patients receiving high doses or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss.

NOTE: The risk of toxic reactions is low in patients with normal renal function who do not receive Nebcin in higher doses or for longer periods of time than those recommended.

Other reported adverse reactions possibly related to Nebcin include increased serum transaminase (SGOT, SGPT) and increased serum bilirubin; anemia, granulocytopenia, and thrombocytopenia; and fever, rash, itching, urticaria, nausea, vomiting, headache, and lethargy.

Suggested Dosage Guides—I.M./I.V.:

The usual duration of treatment is seven to ten days.

Usual dosage for adults, children, and older infants (normal renal function)—

3 mg/kg/day administered in three equal doses every eight hours. In life-threatening situations, the dosage may be increased up to 5 mg/kg/day administered in three or four equal doses. This dosage should be reduced to 3 mg/kg/day as soon as clinically indicated. (Refer to Table 1 for dosage schedule.)

Dosage for neonates up to one week of age (normal renal function)—

Up to 4 mg/kg/day may be given in two equal doses every 12 hours.

Dosage guidelines for adult or pediatric patients with reduced renal function—

After a loading dose of 1 mg/kg, subsequent dosage must be adjusted either with reduced doses at eight-hour intervals or with normal doses at prolonged intervals. To determine the reduced dose at eight-hour intervals, see the convenient nomogram in the package literature.* To calculate normal dosage at prolonged intervals (if the creatinine clearance rate is not available and the patient's condition is stable), the following formula may be used:

1 mg/kg q (6 × serum creatinine) h

Neither regimen should be used when dialysis is being performed.

I. V. Administration—The usual volume of diluent for adults is 50 to 100 ml. For children, the volume of diluent should be proportionately less than for adults. The diluted solution usually should be infused over a period of 20 to 60 minutes.

Table 1. Dosage Schedule Guide for Adults with Normal Renal Function
(Dosage at Eight-Hour Intervals)

For Patient Weighing		Usual Dose for Serious Infections 1 mg/kg q 8 h (Total, 3 mg/kg/day)		Maximum Dose for Life-Threatening Infections **(Reduce as soon as possible)** 1.66 mg/kg q 8 h (Total, 5 mg/kg/day)	
kg	lb	**mg/dose** q 8 h	**ml/dose†**	**mg/dose** q 8 h	**ml/dose†**
120	264	120 mg	3 ml	200 mg	5 ml
115	253	115 mg	2.9 ml	191 mg	4.75 ml
110	242	110 mg	2.75 ml	183 mg	4.5 ml
105	231	105 mg	2.6 ml	175 mg	4.4 ml
100	220	100 mg	2.5 ml	166 mg	4.2 ml
95	209	95 mg	2.4 ml	158 mg	4 ml
90	198	90 mg	2.25 ml	150 mg	3.75 ml
85	187	85 mg	2.1 ml	141 mg	3.5 ml
80	176	80 mg	2 ml	133 mg	3.3 ml
75	165	75 mg	1.9 ml	125 mg	3.1 ml
70	154	70 mg	1.75 ml	116 mg	2.9 ml
65	143	65 mg	1.6 ml	108 mg	2.7 ml
60	132	60 mg	1.5 ml	100 mg	2.5 ml
55	121	55 mg	1.4 ml	91 mg	2.25 ml
50	110	50 mg	1.25 ml	83 mg	2.1 ml
45	99	45 mg	1.1 ml	75 mg	1.9 ml
40	88	40 mg	1 ml	66 mg	1.6 ml

†Applicable to all product forms except Nebcin, Pediatric, Injection (see How Supplied)

How Supplied: Ampoules (Vials) Nebcin® (tobramycin sulfate, Lilly), Injection, 80 mg (equivalent to tobramycin) per 2 ml, 2 ml, rubber-stoppered, in packages of 1 and Traypaks™ (multivial cartons, Lilly) of 25.

Ampoules (Vials) Nebcin, Pediatric, Injection, 20 mg (equivalent to tobramycin) per 2 ml, 2 ml, rubber-stoppered, in packages of 1.

Hyporets® (disposable syringes, Lilly) Nebcin, Injection, 60 mg (equivalent to tobramycin) per 1.5 ml, 1.5 ml, and 80 mg (equivalent to tobramycin) per 2 ml, 2 ml, in packages of 24.

Each ml also contains 5 mg phenol as a preservative, 3.2 mg sodium bisulfite, 0.1 mg edetate disodium, and water for injection, q.s. Sulfuric acid and/or sodium hydroxide may have been added to adjust the pH. [030476C]

Additional information available to the profession on request from Eli Lilly and Company,
Indianapolis, Indiana 46206.

Lilly
Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

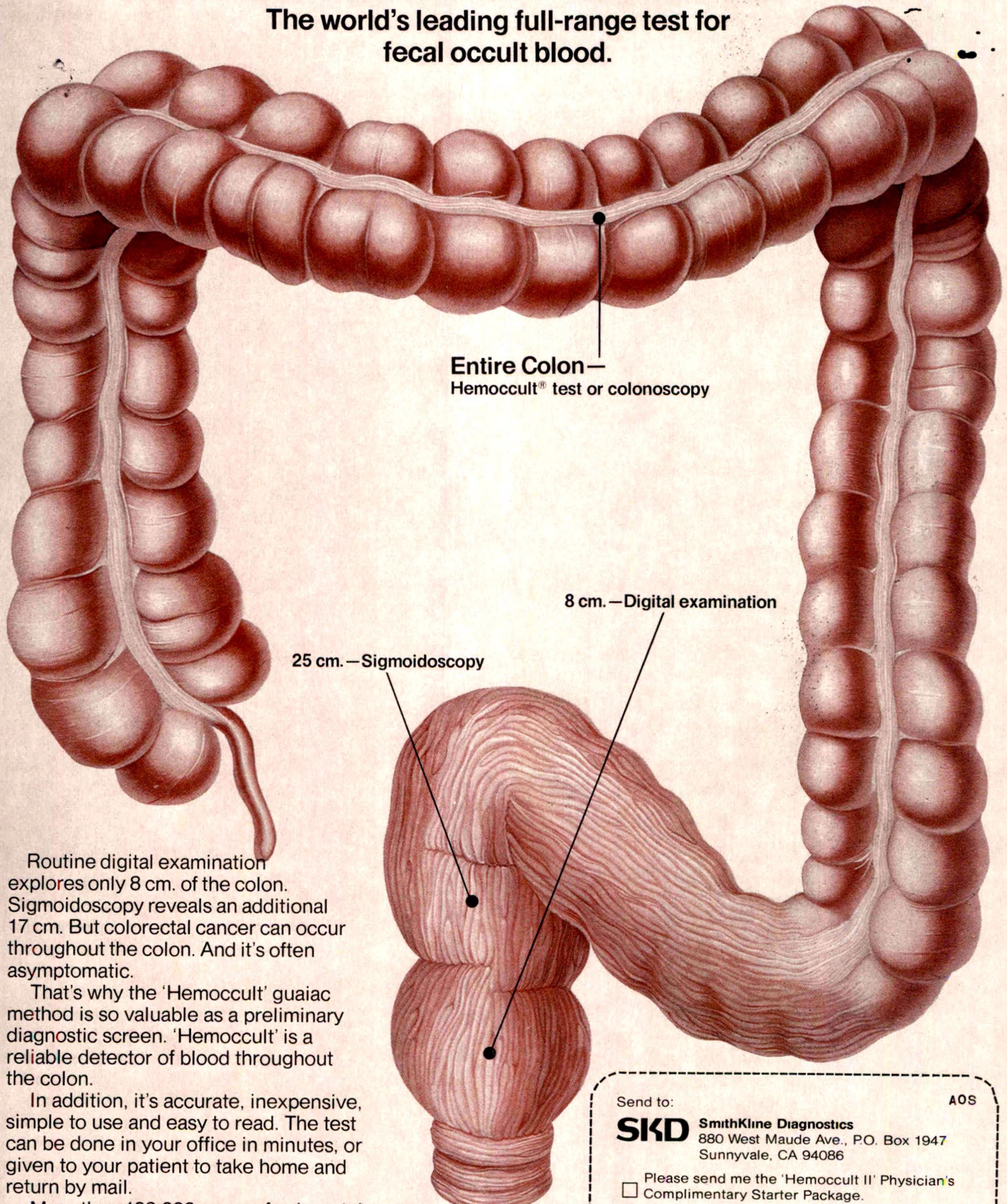
800646

---

*An alternate rough guide for determining reduced dosage at eight-hour intervals (for patients whose steady-state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine.

Hemoccult®

The world's leading full-range test for fecal occult blood.



Routine digital examination explores only 8 cm. of the colon. Sigmoidoscopy reveals an additional 17 cm. But colorectal cancer can occur throughout the colon. And it's often asymptomatic.

That's why the 'Hemoccult' guaiac method is so valuable as a preliminary diagnostic screen. 'Hemoccult' is a reliable detector of blood throughout the colon.

In addition, it's accurate, inexpensive, simple to use and easy to read. The test can be done in your office in minutes, or given to your patient to take home and return by mail.

More than 100,000 cases of colorectal cancer will occur in the United States this year. The earlier they are diagnosed, the greater the chances for successful treatment. Send for your free 'Hemoccult' starter package, today.

'Hemoccult' is available through local distributors, nationwide.

Send to:
AOS

SKD **SmithKline Diagnostics**
880 West Maude Ave., P.O. Box 1947
Sunnyvale, CA 94086

☐ Please send me the 'Hemoccult II' Physician's Complimentary Starter Package.

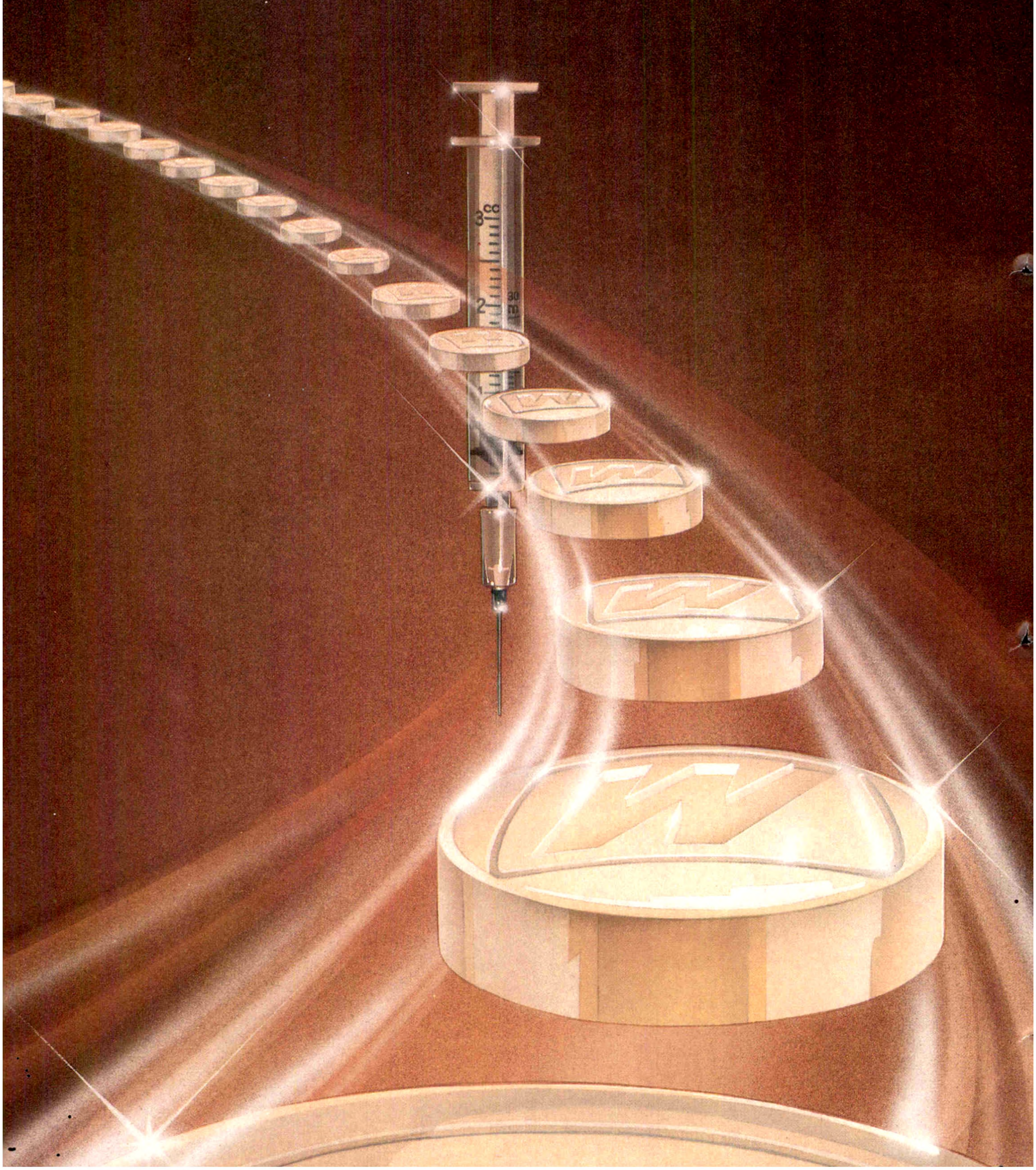
Name ____________________

Address ____________________

City ____________ State ________ Zip ______

Phone ____________________

When the need for injectables is over...help keep your patient free of pain.



Potent – Dependable – Analgesic

Talwin® 50

brand of · equivalent to 50 mg base
pentazocine HCl tablets, NF Ⓘⓥ

A unique agonist/antagonist. Relieves pain as well as 60 mg of codeine.

MILD ANALGESICS OFTEN DON'T WORK

In a double-blind single dose study involving 225 adult inpatients, the comparative efficacy of 650 mg aspirin and 65 mg dextropropoxyphene, was compared to 50 mg of pentazocine for relief of postoperative pain.*

- All patients were suffering from moderate or severe pain.
- Pregnant women as well as patients with known renal, respiratory, cardiac, or hepatic insufficiency were excluded.
- The onset of action of pentazocine was rapid.
- Although aspirin, dextropropoxyphene, and pentazocine produced significant relief from pain, pentazocine was significantly more effective at a half hour.
- Side effects were recorded for 16 patients: in the aspirin group 2 patients complained of drowsiness and 1 of dizziness. In the dextropropoxyphene group 5 patients vomited and 3 patients complained of drowsiness or dizziness, while 5 patients who had received pentazocine complained of dizziness.
- Pentazocine should be an oral analgesic of choice for treatment of postoperative pain.

The advantages of Talwin 50:

The combined agonist/antagonist properties of Talwin 50 make it a drug to be considered, particularly when pain is likely to be of a persistent nature. When such pain exists, the potential for agonist dependency as well as complicating agonist side effects may be reduced by the use of Talwin 50.

Talwin 50 shows infrequent occurrence of certain adverse effects as:

- Severe respiratory depression
- Urinary retention
- Hypotension
- Tachycardia
- Constipation

While others such as nausea and dizziness are more common.

Among RARELY REPORTED REACTIONS are those of a psychiatric nature. Even the most acute CNS reactions—hallucinations (usually visual)—have cleared spontaneously within a period of hours. Withdrawal symptoms after prolonged use of Talwin 50 for the relief of pain have rarely been reported, even when administration was abruptly discontinued. There have been a few reports of dependence with orally administered Talwin 50. Patients with a history of drug dependence should be under close supervision while receiving Talwin 50 orally. See the following important product information as to dependency potential.

For Continuing Postsurgical Pain Control

Talwin® 50

brand of · equivalent to 50 mg base
pentazocine HCl tablets, NF Ⓘⓥ

1 or 2 tablets every three or four hours.

*Kay B: A clinical comparison of orally administered aspirin, dextropropoxyphene and pentazocine in the treatment of postoperative pain. *J Int Med Res* 2:149-152, 1974.

See important product information including warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations, a brief summary of which follows.

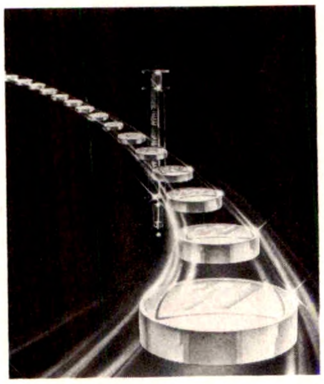
Potent—Dependable—Analgesic

Talwin® 50

brand of · equivalent to 50 mg base
pentazocine HCl tablets, NF Ⓒ IV

Relieves pain of a moderate to severe nature.

Usual initial adult dose is 1 tablet every 3 or 4 hours.



Please consult full prescribing information before prescribing.
A summary follows:
TALWIN 50 is intended for the relief of moderate to severe pain. One 50 mg tablet appears equivalent in analgesic effect to 60 mg (1 gr) of codeine. TALWIN 50 is a weak narcotic antagonist with sedative activity.

Contraindication:
Hypersensitivity to pentazocine.

Warnings:
Drug Dependence. There have been instances of psychological and physical dependence on parenteral pentazocine in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral pentazocine has resulted in withdrawal symptoms. There have been a few reports of dependence and of withdrawal symptoms with orally administered TALWIN 50. Patients with a history of drug dependence should be under close supervision while receiving TALWIN 50 orally. There have been rare reports of possible abstinence syndromes in newborns after prolonged use of TALWIN 50 during pregnancy.

In prescribing TALWIN 50 for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure. TALWIN 50 may elevate cerebrospinal fluid pressure. This may be markedly exaggerated in the presence of head injury, intracranial lesions and a preexisting increase in intracranial pressure. TALWIN 50 may obscure the clinical course of patients with head injuries. TALWIN 50 should be used with extreme caution in such patients and only if its use is deemed essential.

Usage in Pregnancy. Safe use of TALWIN 50 during pregnancy (other than labor) has not been established. Although no teratogenic or embryotoxic effects have been reported in animals, TALWIN 50 should be administered to pregnant patients (other than labor) only when potential benefits outweigh possible hazards, and cautiously in labor of women delivering prematurely.

Acute CNS Manifestations. In therapeutic dosages, rarely, transient hallucinations (usually visual), disorientation, and confusion may occur. Observe such patients carefully and check vital signs. Use caution if the drug is reinstituted since the acute CNS manifestations may recur.

Usage in Children. Not presently recommended under 12.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions:
TALWIN 50 has been rarely reported to cause respiratory depression. It should be used with caution in patients with respiratory depression, severely limited respiratory reserve, bronchospasm, cyanosis, renal or hepatic dysfunction. Caution should also be used with patients prone to convulsive disorders and those about to undergo biliary surgery. As with other strong analgesics, use with caution in patients with myocardial infarction who have nausea or vomiting. Patients previously given narcotics, including methadone, may experience withdrawal symptoms after receiving TALWIN 50.

Adverse Reactions:
Reactions reported after oral administration of TALWIN 50 include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. *CNS effects:* dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations; and rarely tremor, irritability, excitement, tinnitus. *Autonomic:* sweating; infrequently flushing; and rarely chills. *Allergic:* infrequently rash; and rarely urticaria, edema of the face. *Cardiovascular:* infrequently decrease in blood pressure, tachycardia. *Hematologic:* rarely depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia. *Other:* rarely respiratory depression, urinary retention, paresthesia, toxic epidermal necrolysis.

Dosage and Administration:
Adults: The usual initial adult dose is 1 tablet (50 mg) every three or four hours. This may be increased to 2 tablets (100 mg) when needed. Total daily dosage should not exceed 600 mg. Tolerance is rare. Abrupt discontinuance following chronic use has rarely caused withdrawal symptoms.

Overdosage:
Oxygen, parenteral naloxone, intravenous fluids, vasopressors, assisted or controlled ventilation, and other supportive measures should be employed as indicated.

WNT5594

Winthrop
90 PARK AVENUE
NEW YORK, N.Y. 10016

INDEX TO ADVERTISERS

PHARMACEUTICAL SUPPLIES

Beecham Laboratories
  Ticar ....14A thru 16A
Boehringer Ingelheim Limited
  Dulcolax 11A
Breon Laboratories, Inc.
  Marcaine 58A,59A
Bristol Laboratories
  Cefadyl ....44A thru 46A
  Kantrex..................... 60A,61A
Burroughs Wellcome Company
  Empirin Compound c
    Codeine ....Cover IV
Eaton Laboratories
  Vivonex.........................8A,9A
Endo Laboratories
  Nubain ....49A thru 54A
  Percocet..................... 62A,63A
  Percodan .... 74A,Cover III
Flint Laboratories
  Travase..........................33A
Ives Laboratories, Inc.
  Synalgos 17A
Knoll Pharmaceuticals
  Dilaudid .... Cover II
  Vicodin ....30A thru 32A
Eli Lilly Laboratories
  Keflin 27,28
  Nebcin ....66A thru 68A
McNeil Laboratories
  Tylox 55A
Mead Johnson Pharmacuetical Division
  Colace...........................65A
  Megace..................37A thru 40A
  Sustacal 1A
Merck Sharp & Dohme
  Mefoxin 18A,19A
Ortho Diagnostics, Inc.
  Chromogenic Antithrombin III
    Assay 41A
Parke Davis Company
  Chloromycetin .... 4A thru 6A
Searle Laboratories
  Metamucil 48A
Smith Kline & French Laboratories
  Compazine.................. 22A,23A
  Hemoccult 69A
  Tagamet 34A,35A
USV Laboratories
  MVI 42A,43A
Winthrop Laboratories
  Talwin Injectable ....24A thru 26A
  Talwin 50................70A thru 72A

SUPPLIES & EQUIPMENT

Carolina Medical Electronics, Inc.
  Electromagnetic Blood Flowmeter ..16A
Ethicon, Inc.
  Prolene Sutures..................29A
  Vicryl Sutures............... 56A,57A
3M Company
  Steri-Strip Skin Closures...........13A
The Purdue Frederick Company
  Betadine Surgical Products.......... 2A
Reed & Carnrick
  Cortifoam................... 20A,21A

MISCELLANEOUS

Grune & Stratton..................28A
Harper & Row Publishers 32A
Jesse Jones Box Corporation........57A
J. B. Lippincott Company.......18A,36A,
  42A,47A,48A,61A,62A,64A
Xerox University Microfilms
  International 74A

You can now order article reprints from this publication

University Microfilms International, in cooperation with publishers of this journal, offers a highly convenient Article Reprint Service. Single articles or complete issues can now be obtained in their original size (up to 8½ x 11 inches). For more information please complete and mail the coupon below.

ARTICLE REPRINT SERVICE
University Microfilms International

☐ YES! I would like to know more about the Article Reprint Service. Please send me full details on how I can order.
☐ Please include catalogue of available titles.

Name ______________ Title ______________
Institution/Company ______________
Department ______________
Address ______________
City ______________ State ______________ Zip ______

Mail to: **University Microfilms International**
Article Reprint Service
300 North Zeeb Road
Ann Arbor, Michigan 48106

Tablets
PERCODAN®
oxycodone with APC Ⓒ

Tablets
PERCODAN®-Demi
oxycodone with APC Ⓒ

Brief Summary of Prescribing Information

INDICATIONS For the relief of moderate to moderately severe pain

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN* and PERCODAN*-Demi, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN* and PERCODAN*-Demi are subject to the Federal Controlled Substances Act

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN* and PERCODAN*-Demi should be cautioned accordingly

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN* and PERCODAN*-Demi may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore PERCODAN* and PERCODAN*-Demi should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards

Usage in children PERCODAN* should not be administered to children. PERCODAN*-Demi, containing half the amount of oxycodone, can be considered

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN* and PERCODAN*-Demi or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions

Special risk patients PERCODAN* and PERCODAN*-Demi should be given with caution to certain patients such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down

Other adverse reactions include euphoria, dysphoria, constipation and pruritus

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCODAN* and PERCODAN*-Demi are given orally.

PERCODAN* The usual adult dose is one tablet every 6 hours as needed for pain

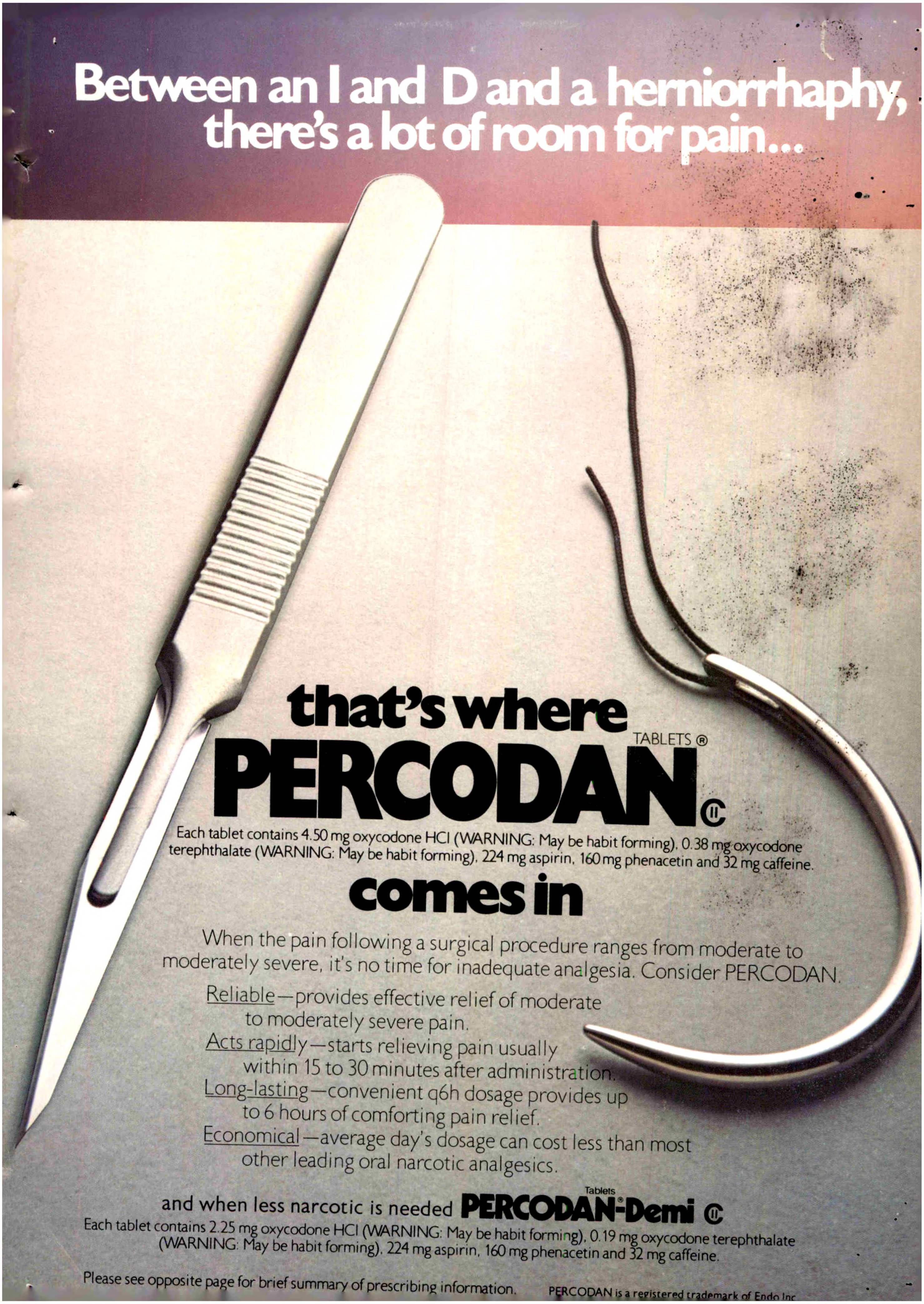
PERCODAN*-Demi Adults—One or two tablets every six hours. Children 12 years and older—One-half tablet every six hours. Children 6 to 12 years—One-quarter tablet every six hours. PERCODAN*-Demi is not indicated for children under 6 years of age

DRUG INTERACTIONS The CNS depressant effects of PERCODAN* and PERCODAN*-Demi may be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents

DEA Order Form Required. 6074-1-6078-IBS

Endo Inc. DUPONT
Manati, Puerto Rico
Subsidiary of Endo Laboratories Inc.
Subsidiary of the DuPont Company



Between an I and D and a herniorrhaphy, there's a lot of room for pain...

that's where PERCODAN TABLETS ® ⓒ

Each tablet contains 4.50 mg oxycodone HCl (WARNING: May be habit forming), 0.38 mg oxycodone terephthalate (WARNING: May be habit forming), 224 mg aspirin, 160 mg phenacetin and 32 mg caffeine.

comes in

When the pain following a surgical procedure ranges from moderate to moderately severe, it's no time for inadequate analgesia. Consider PERCODAN.

Reliable—provides effective relief of moderate to moderately severe pain.

Acts rapidly—starts relieving pain usually within 15 to 30 minutes after administration.

Long-lasting—convenient q6h dosage provides up to 6 hours of comforting pain relief.

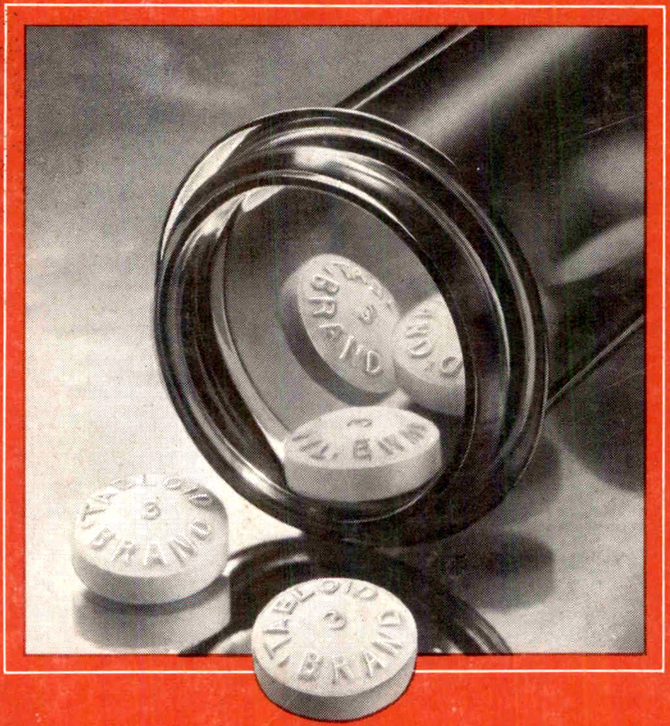
Economical—average day's dosage can cost less than most other leading oral narcotic analgesics.

and when less narcotic is needed **PERCODAN®-Demi Tablets** ⓒ

Each tablet contains 2.25 mg oxycodone HCl (WARNING: May be habit forming), 0.19 mg oxycodone terephthalate (WARNING: May be habit forming), 224 mg aspirin, 160 mg phenacetin and 32 mg caffeine.

Please see opposite page for brief summary of prescribing information.

PERCODAN is a registered trademark of Endo Inc.



EMPIRIN® COMPOUND c̄ CODEINE

Each tablet contains: aspirin, 227 mg; phenacetin, 162 mg; and caffeine, 32 mg; plus codeine phosphate in one of the following strengths: #**4**—60 mg (gr 1); #**3**—30 mg (gr ½); #**2**—15 mg (gr ¼); and #**1**—7.5 mg (gr ⅛), (Warning—may be habit-forming).

CIII

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

Acc.
5.3.80

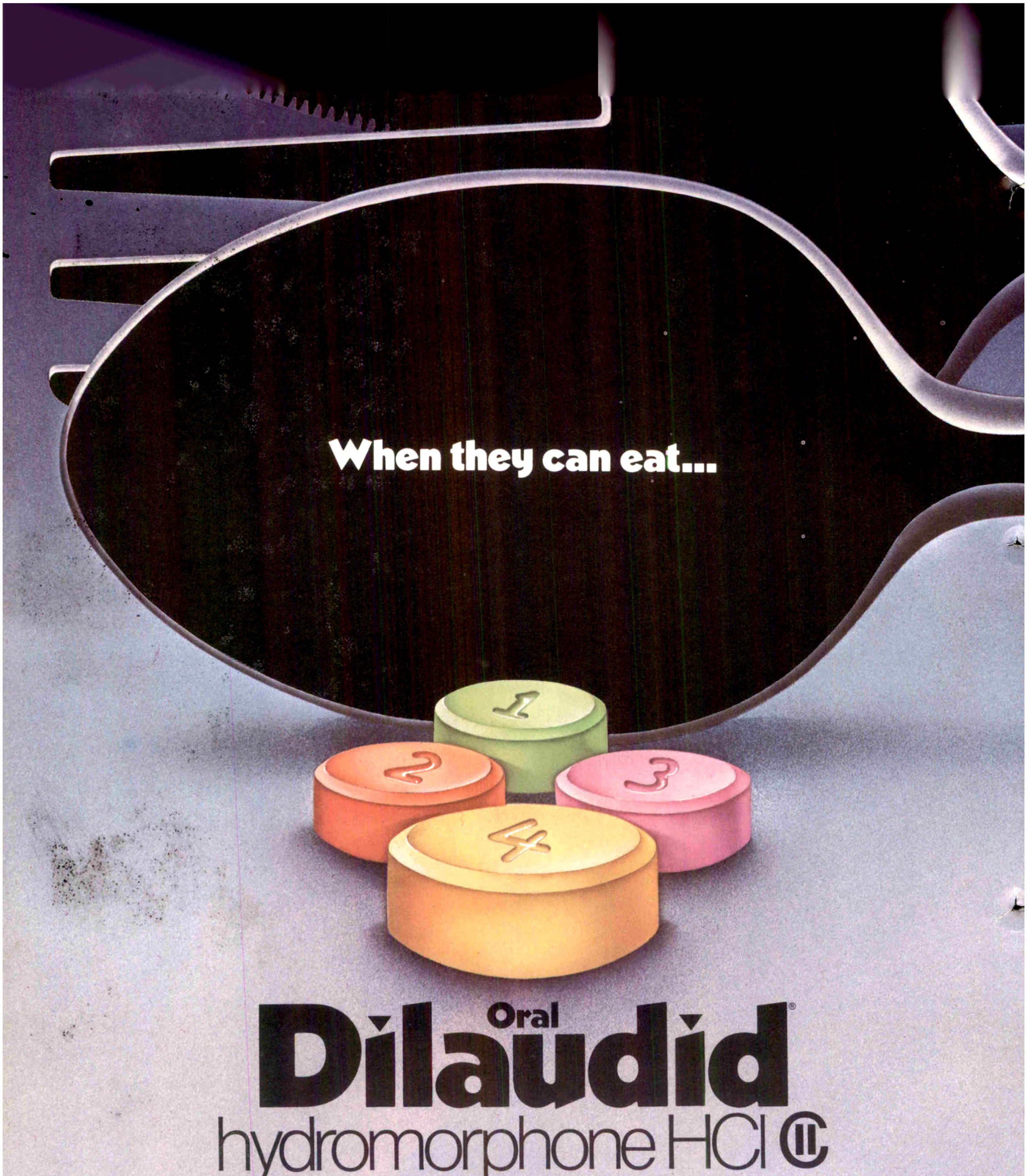
AUGUST 1979 • VOL. 190, NO. 2
ISSN 0003-4932 ANSUA5

ANNALS
of
SURGERY

A Monthly Review of
Surgical Science and Practice
Since 1885

UNIVERSITY COLLEGE OF MEDICINE
LIBRARY

J. B. LIPPINCOTT COMPANY
PHILADELPHIA • TORONTO



Oral
Dilaudid®
hydromorphone HCl CII

The first step after injectables in post-op analgesia.

Description: Dilaudid is hydromorphone, a hydrogenated ketone of morphine.
Indications: For relief of moderate to severe pain.
Contraindications: Suspected increased intracranial pressure, status asthmaticus.
Warnings: May be habit forming with a potential for addiction equivalent to morphine in equi-analgesic doses. Tolerance may also occur. As with all narcotics, use in early pregnancy only when expected benefits outweigh risks.
Adverse Effects: Nausea, vomiting, diarrhea, constipation, anorexia and somnolence may occur although unlikely with appropriate dose selection.
Dosage and Administration: Dosage must be individualized. The usual adult dose is 2 mg every 4-6 hours, as necessary, for moderate to moderately severe pain. For more severe pain, 3-4 mg or more every 4-6 hours, as necessary, may be required.
Treatment of Overdosage: If overdosage is treated within an hour, emesis and gastric lavage should be attempted. Special attention should be given to respiration and, if depression occurs, it may be antagonized by the use of naloxone hydrochloride (Narcan®)—Endo, nalorphine hydrochloride (Nalline®)—Merck Sharp & Dohme or levallorphan tartrate (Lorfan®)—Roche, as recommended by the manufacturer. Other supportive measures should be applied when indicated.
How Supplied: Dilaudid HCl color coded tablets (NOT FOR INJECTION) imprinted with K logo on one side and potency on other side as follows: green—1 mg; orange—2 mg; pink—3 mg and yellow—4 mg. Available in: 1 mg—bottles of 100 (NDC #0044-1021-02), 2 mg—bottles of 100 (NDC #0044-1022-02) and 500 (NDC #0044-1022-03), 3 mg—bottles of 100 (NDC #0044-1023-02), 4 mg—bottles of 100 (NDC #0044-1024-02) and 500 (NDC #0044-1024-03).

Knoll Pharmaceutical Company
Whippany, New Jersey 07981

Member Company, Certified Medical Representative Institute, Inc.

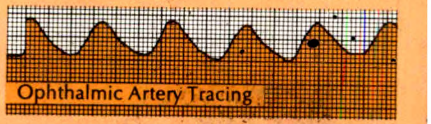
PULSE VOLUME RECORDER (PVR®)*

The NON-INVASIVE Clinical Vascular Laboratory

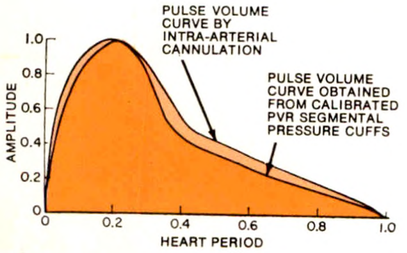
An Extensively Documented Clinical Procedure for the Quantitative Evaluation of Peripheral Vascular Disease:

Arterial — Venous — Cerebral

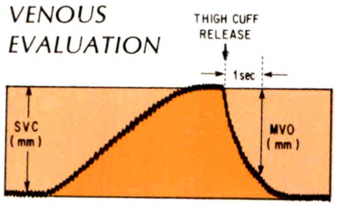
Excellent Long-term Reproducibility and Calibrated Accuracy by Quantitative Segmental Cuff Technique



Ophthalmic artery pressure is read directly on the OPG Attachment of the PVR for the evaluation of collateral circulation to each eye, and its respective cerebral hemisphere.



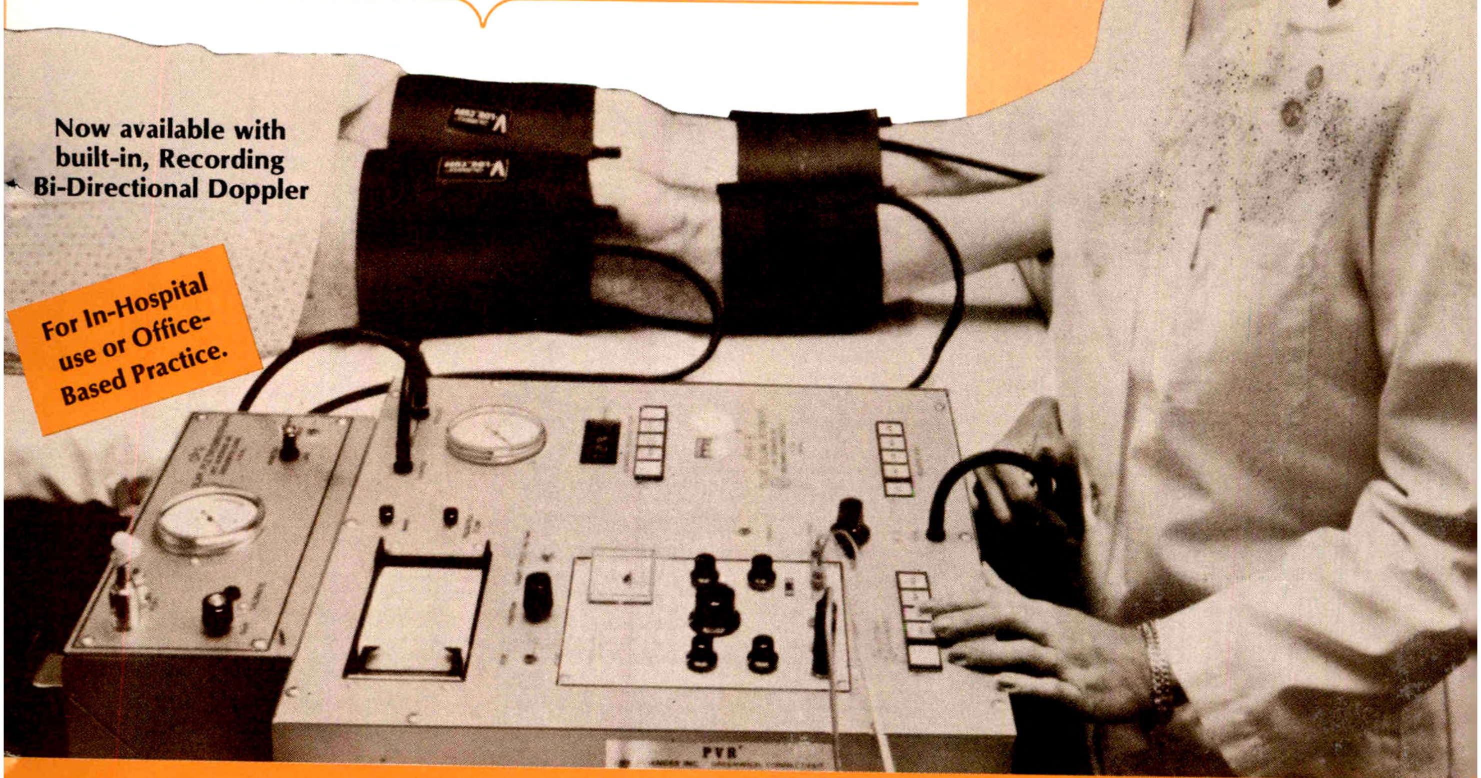
Comparison of pressure contours obtained with the PVR and direct cannulation of the common femoral artery.



A 15-point scale provides approximately 5% false (+) and 2 % false (-).

Total Segmental Perfusion (primary vessel plus collaterals) is accurately documented at the thigh-calf-ankle-metatarsal level and digits. The built-in Doppler facilitates the measurement of pressures along the arterial tree.

The COMBINED information of segmental PVR recordings and systolic pressure gradient establishes a clinically accurate picture of functional perfusion.



Now available with built-in, Recording Bi-Directional Doppler

For In-Hospital use or Office-Based Practice.

Reimbursement for In- and Out-Patients under: Various non-profit hospital and medical-surgical service plans
• Medicare • Veterans Benefits • Commercial Insurance Companies.

References, bibliography, and details on request.

Life Sciences Inc.
270 Greenwich Avenue
Greenwich, Connecticut 06830 U.S.A.

* As Developed by The

Osborn

Nip it in the gut.

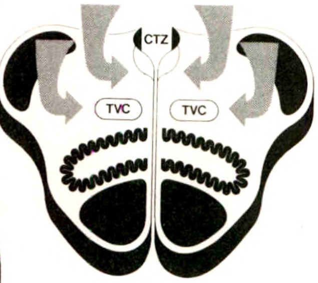
Torecan can help control nausea and vomiting with dual action:*
1) against circulating emetics (at the CTZ)
2) against emetic sights, emotions, and organ insults (at the TVC)

In using Torecan, the physician should consider the adverse reactions which are associated with the drug specifically and phenothiazines generally.**

- It's not for sedative use.
- It's not intended as a tranquilizer.
- It's not an antihistamine.
- It's not intended for psychotic symptoms.

*As shown in animal studies; TVC – True Vomiting Center, CTZ – Chemoreceptor Trigger Zone.

**Please see brief summary for detailed information concerning potential adverse reactions.



Torecan®
(thiethylperazine)

Injectable—10 mg/2ml (thiethylperazine malate, NF)
for IM injection only

Suppositories—10 mg (thiethylperazine maleate, NF)

Tablets—10 mg (thiethylperazine maleate, NF)

Torecan® (thiethylperazine)
Tablets, Suppositories and Injection

Contraindications: Severe CNS depression, comatose states, and in patients who have demonstrated a hypersensitivity to phenothiazines (e.g., blood dyscrasias, jaundice). Because severe hypotension has been reported after the intravenous administration of phenothiazines, this route of administration is contraindicated. The drug is contraindicated in pregnancy.

Warnings: Phenothiazines are capable of potentiating CNS depressants as well as atropine and phosphorous insecticides. The drug may impair mental and/or physical ability required in the performance of potentially hazardous tasks such as driving a car or operating machinery.

Postoperative Nausea and Vomiting: When used to control postoperative nausea and vomiting in patients undergoing elective surgical procedures, restlessness and postoperative CNS depression during anesthesia recovery may occur. Possible postoperative complications of a severe degree of any of the known reactions of this class of drug must be considered. Postural hypotension may occur after an initial injection, rarely with the tablet or suppository. Do not use with epinephrine in the treatment of drug-induced hypotension as phenothiazines may induce a reversed epinephrine effect. The most suitable vasoconstrictor agents are levarterenol and phenylephrine. The use of Torecan has not been studied following intracardiac and intracranial surgery. Not recommended for use in children under 12 years of age, or in nursing mothers since safety and efficacy have not been established.

Precautions: Convulsions and abnormal movements such as extrapyramidal symptoms have occurred. The varied extrapyramidal symptom complex is more likely to occur in young adults and children. Extrapyramidal effects must be treated by reduction of dosage or cessation of medication. For treatment of nausea and/or vomiting associated with anesthesia and surgery, the drug should be administered by deep intramuscular injection at or shortly before the termination of anesthesia.

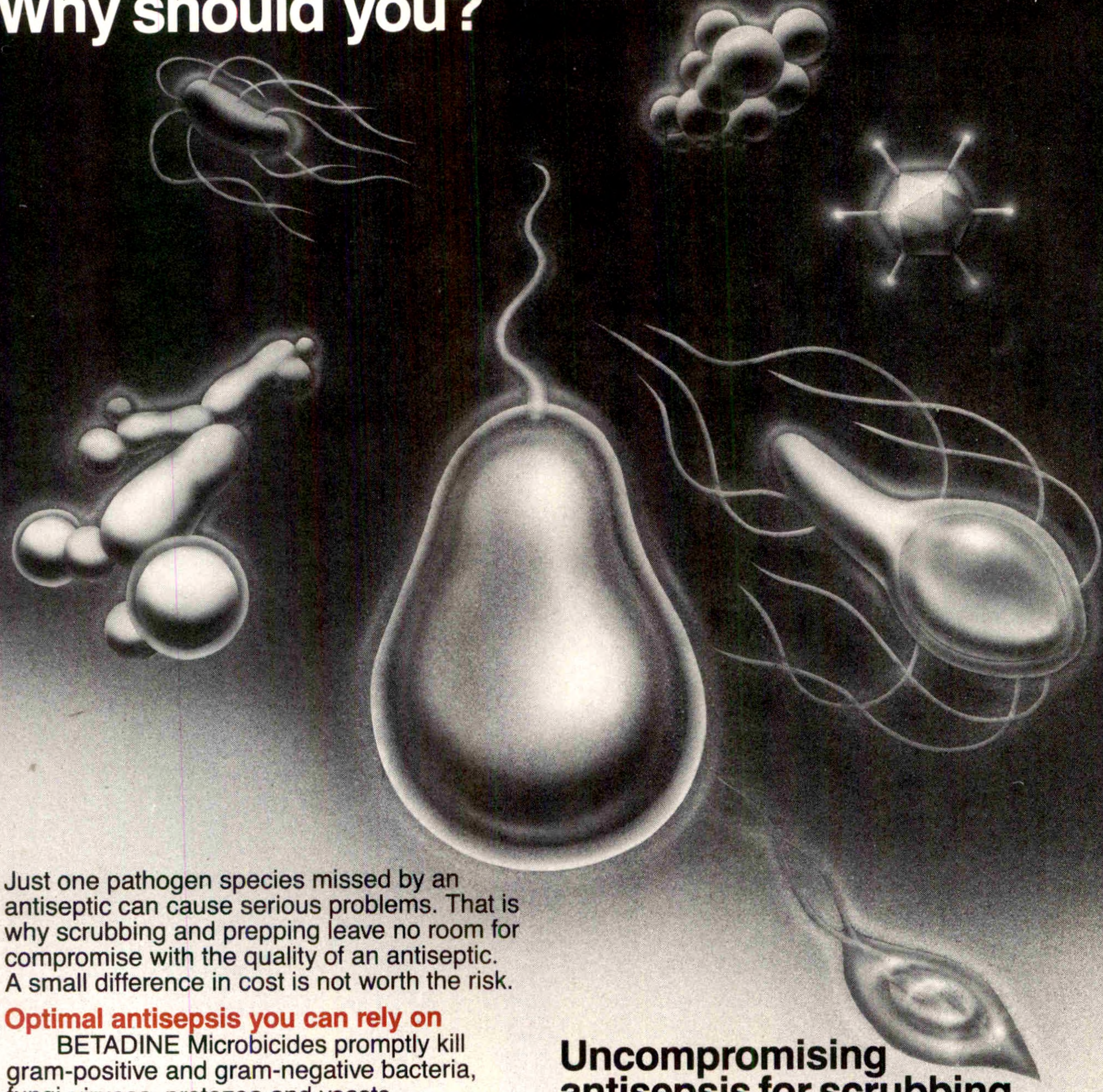
Adverse Reactions: CNS: convulsions, extrapyramidal symptoms such as dystonia, torticollis, oculogyric crisis, akathisia and gait disturbances, occasional cases of dizziness, headache, fever and restlessness have been reported. Drowsiness may occur initially on injection but is usually alleviated by a reduction in dosage. Dryness of the mouth and nose, blurred vision, tinnitus; sialorrhea and altered gustatory sensation. Peripheral edema of the arms, hands and face. Cholestatic jaundice; cerebral vascular spasm and trigeminal neuralgia have been reported occasionally. The following have occurred with phenothiazine derivatives and should be considered: agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia, pancytopenia, eosinophilia, leukocytosis; miosis, obstipation, anorexia, paralytic ileus; erythema, exfoliative dermatitis and contact dermatitis; jaundice, biliary stasis. Hypotension, rarely leading to cardiac arrest; ECG changes. Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia, some of which have persisted for several months or years especially in patients of advanced age with brain damage. Menstrual irregularities, altered libido, gynecomastia, weight gain; false positive pregnancy tests. Urinary retention, incontinence; fever, laryngeal edema and angioneurotic edema, asthma. Hyperpyrexia, behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses and toxic confusional states. ECG changes. While there is no evidence that ECG changes are in any way precursors of any significant disturbance of cardiac rhythm, sudden and unexpected deaths apparently due to cardiac arrest have been reported in a few instances in hospitalized psychotic patients previously showing characteristic ECG changes. A peculiar skin-eye syndrome, which is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea, has also been recognized as a side effect following long-term treatment. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported.

Drug Interactions: Phenothiazines are capable of potentiating CNS depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorous insecticides. The drug may induce a reversed epinephrine effect on occasion.

For complete details, please see full prescribing information.

Boehringer Ingelheim
Boehringer Ingelheim Ltd.
Ridgefield, CT 06877

Pathogens don't compromise. Why should you?



Just one pathogen species missed by an antiseptic can cause serious problems. That is why scrubbing and prepping leave no room for compromise with the quality of an antiseptic. A small difference in cost is not worth the risk.

Optimal antisepsis you can rely on

BETADINE Microbicides promptly kill gram-positive and gram-negative bacteria, fungi, viruses, protozoa and yeasts.

BETADINE Microbicides have been documented specifically by name—and in the same formulations you employ in practice—in over 650 published reports encompassing thousands of clinical procedures.

BETADINE Microbicides were also chosen by NASA for disinfection procedures in Apollo splashdowns and in the Skylab mission.

BETADINE Microbicides for surgical confidence

_____ BETADINE Surgical Scrub*—for surgical scrubbing and patient degerming.

_____ BETADINE Solution or BETADINE Aerosol Spray—for patient prepping and postoperative antisepsis on incisions.

Uncompromising antisepsis for scrubbing and prepping

BETADINE® Surgical Scrub
BETADINE® Solution
BETADINE® Aerosol Spray

*In the rare instances of local irritation or sensitivity, discontinue use by the individual.

Purdue Frederick
©Copyright 1979, The Purdue Frederick Company/Norwalk, CT 06856

A9458 214679

Annals of Surgery

A Monthly Review of Surgical Science and Practice

Also the official publication of
THE AMERICAN SURGICAL ASSOCIATION
THE SOUTHERN SURGICAL ASSOCIATION
PHILADELPHIA ACADEMY OF SURGERY
NEW YORK SURGICAL SOCIETY

EDITORIAL AND ADVISORY BOARD

DAVID C. SABISTON, JR., M.D., *Chairman*
Durham, N.C.

J. WESLEY ALEXANDER, M.D.
Cincinnati, O.
WILLIAM A. ALTEMEIER, M.D.
Cincinnati, O.
W. GERALD AUSTEN, M.D.
Boston, Mass.
HENRY T. BAHNSON, M.D.
Pittsburgh, Pa.
WARREN H. COLE, M.D.
Asheville, N.C.
MICHAEL E. DE BAKEY, M.D.
Houston, Tex.
STANLEY J. DUDRICK, M.D.
Houston, Tex.
J. ENGLEBERT DUNPHY, M.D.
San Francisco, Calif.
PAUL A. EBERT, M.D.
San Francisco, Calif.
ERIC W. FONKALSRUD, M.D.
Los Angeles, Calif.
FRANK L. A. GERBODE, M.D.
San Francisco, Calif.
FRANK GLENN, M.D.
New York, N.Y.
FRASER N. GURD, M.D.
Ottawa, Canada
OLGA M. JONASSON, M.D.
Chicago, Ill.

WILLIAM P. LONGMIRE, JR., M.D.
Los Angeles, Calif.
LEONARD D. MILLER, M.D.
Philadelphia, Pa.
FRANCIS D. MOORE, M.D.
Boston, Mass.
WILLIAM H. MULLER, JR., M.D.
Charlottesville, Va.
JOHN S. NAJARIAN, M.D.
Minneapolis, Minn.
JONATHAN E. RHOADS, M.D.
Philadelphia, Pa.
PAUL S. RUSSELL, M.D.
Boston, Mass.
JOHN A. SCHILLING, M.D.
Seattle, Wash.
G. THOMAS SHIRES, M.D.
New York, N.Y.
HARRIS B. SHUMACKER, JR., M.D.
Indianapolis, Ind.
DAVID B. SKINNER, M.D.
Chicago, Ill.
FRANK C. SPENCER, M.D.
New York, N.Y.
SAMUEL A. WELLS, JR., M.D.
Durham, N.C.

Emeritus Members

William F. Rienhoff, Jr., Baltimore, Md., John D. Stewart, M.D., Boca Raton, Fla.

J. B. LIPPINCOTT COMPANY, *Publishers*
Philadelphia and Toronto

Annals of Surgery (ISSN 0003-4932) is published monthly for $27.00 per year for the United States and its possessions; resident rate (U.S. only) $19.00; all other countries $37.00; by J. B. Lippincott Co., East Washington Square, Philadelphia, PA 19105. Second-class postage paid at Philadelphia, PA and at additional mailing offices.
POSTMASTER: Send address changes to Annals of Surgery, J. B. Lippincott Co.,
East Washington Square, Philadelphia, PA.
Single copies $5.00. Copyright © 1979 J. B. Lippincott Co. Printed in U.S.A.

Bacteroides

may be implicated in a number of clinical situations, including . . .

- septic abortions
- deep wounds
- bacteremia
- metastatic or other abscesses in association with thromboembolic phenomena

Sensitivity testing is always recommended prior to instituting therapy with Chloromycetin (chloramphenicol). However, in some situations, it may be necessary to administer Chloromycetin before sensitivity tests have been completed.

Bacteroides are the most prevalent microbial flora of man. They are anaerobic, aero-intolerant, nonsporeforming, nonmotile, gram-negative bacilli. They most often appear in mixed infections, and are highly opportunistic. Further, they are very difficult to culture.

Under normal conditions, bacteroides are benign. But in infectious situations they can be extremely virulent.

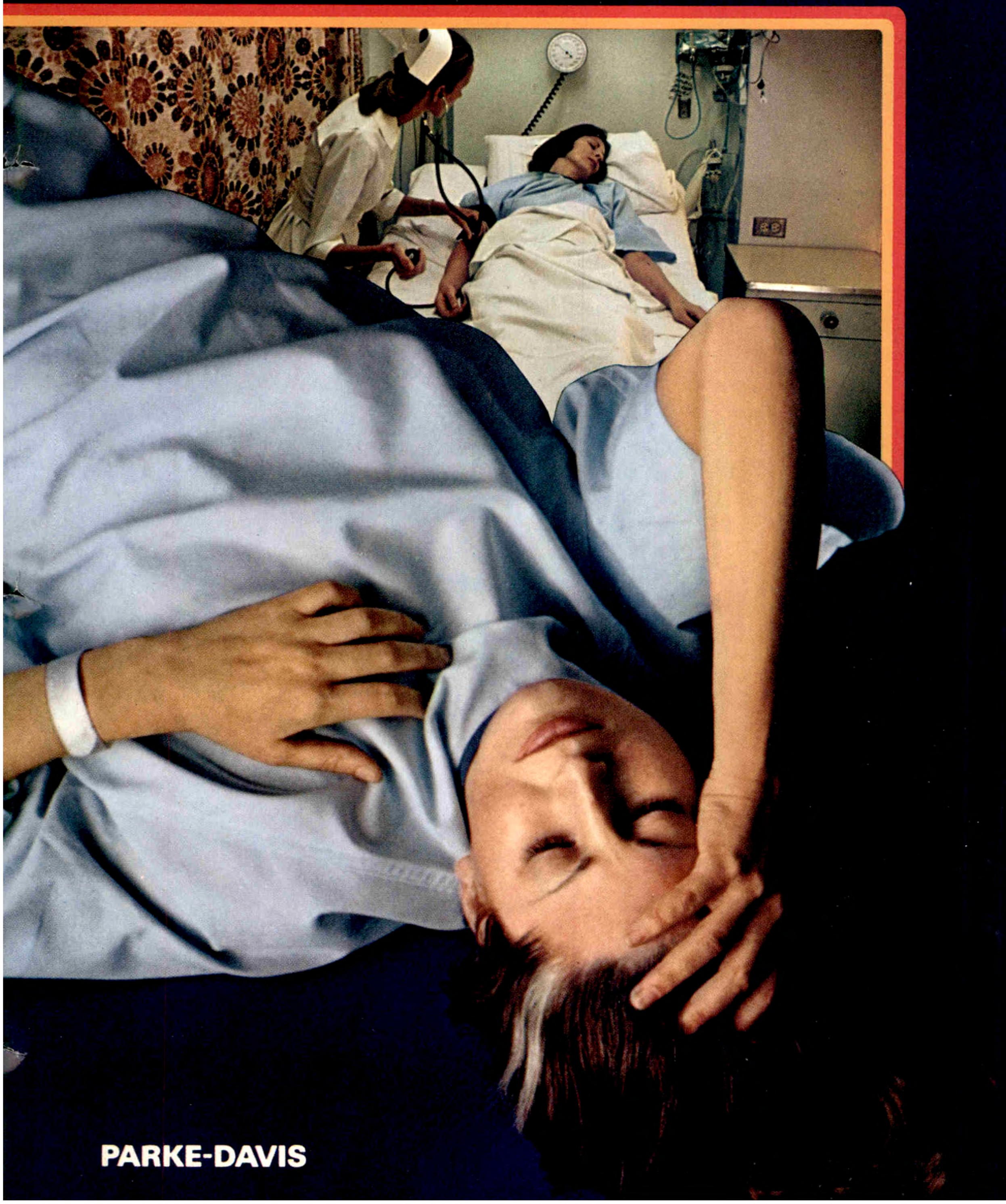
Fortunately, most bacteroides infections are susceptible to Chloromycetin (chloramphenicol) therapy. Yet, all too often their presence goes undetected. So today, many authorities recommend early—and vigorous—treatment with Chloromycetin when the clinical impression suggests that a *Bacteroides* infection is present.

Chloromycetin must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated.

But when bacteroides are implicated, Chloromycetin (chloramphenicol) therapy may well be the conservative course. For, in such situations, the benefits-to-risk ratio with Chloromycetin is very favorable.

See next page for full prescribing information.

Bacteroides...
often an indication for
CHLOROMYCETIN®
(chloramphenicol) Sodium Succinate



PARKE-DAVIS

Prescribing information—Chloromycetin (chloramphenicol) Sodium Succinate
For intravenous administration

> ### WARNING
> **Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the Indications section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.***
>
> **Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.**

IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

CHLORAMPHENICOL SODIUM SUCCINATE IS INTENDED FOR INTRAVENOUS USE ONLY. IT HAS BEEN DEMONSTRATED TO BE INEFFECTIVE WHEN GIVEN INTRAMUSCULARLY.

1. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously.
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for*, serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see Indications section).

Each gram (10 ml of a 10% solution) of chloramphenicol sodium succinate contains approximately 52 mg (2.25 mEq) of sodium.

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group, and *Vibrio cholerae*. It is particularly active against *Salmonella typhi* and *Hemophilus influenzae*. The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every six hours for eight doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/ml one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/ml after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/ml over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8% to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/ml in patients receiving divided doses of 50 mg/kg/day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

In accord with the concepts in the Warning Box and this Indications section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present; *in vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by *in vitro* studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in the Warning Box above.

1. Acute infections caused by *S typhi**

   It is not recommended for the routine treatment of the typhoid carrier state.
2. **Serious infections caused by susceptible strains in accordance with the concepts expressed above.**
   - a) *Salmonella* species
   - b) *H influenzae*, specifically meningeal infections
   - c) Rickettsia
   - d) Lymphogranuloma-psittacosis group
   - e) Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
   - f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents
3. Cystic fibrosis regimens

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.*

PRECAUTIONS

1. Base line blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.
2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.
3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.
4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.
5. There are no studies to establish the safety of this drug in pregnancy.
6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).
7. Precaution should be used in therapy of premature and full-term infants to avoid gray syndrome toxicity. (See Adverse Reactions.) Serum drug levels should be carefully followed during therapy of the newborn infant.
8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.
9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose-related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes, and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding (1) the size of the population at risk, (2) the total number of drug-associated dyscrasias, and (3) the total number of nondrug-associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the gray syndrome. One case of gray syndrome has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month-old infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

- a) In most cases, therapy with chloramphenicol had been instituted within the first 48 hours of life.
- b) Symptoms first appeared after three to four days of continued treatment with high doses of chloramphenicol.
- c) The symptoms appeared in the following order:
  - (1) abdominal distension with or without emesis;
  - (2) progressive pallid cyanosis;
  - (3) vasomotor collapse, frequently accompanied by irregular respiration;
  - (4) death within a few hours of onset of these symptoms.
- d) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
- e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/ml after repeated doses).
- f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the intravenous form because adequate blood levels are achieved with chloramphenicol by mouth.

The following method of administration is recommended:

Intravenously as a 10% (100 mg/ml) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 ml of an aqueous diluent such as water for injection or 5% dextrose injection.

DOSAGE

Adults

Adults should receive 50 mg/kg/day in divided doses at six-hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg/kg/day divided into four doses at six-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (eg, bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants

(See section titled Gray Syndrome under Adverse Reactions.)

A total of 25 mg/kg/day in four equal doses at six-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into four doses at six-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

HOW SUPPLIED

NDC 0071-1089-10 (Steri-Vial® No. 57)

Chloromycetin (chloramphenicol) Sodium Succinate is supplied as a dried powder in Steri-Vials (rubber-diaphragm-capped vials). When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per milliliter (1 g/10 ml). Available in packages of 10 vials.

CHLOROMYCETIN, brand of chloramphenicol. Reg US Pat Off RJ

PD-JA-1280-2-P (2-75)

PARKE-DAVIS, Division of Warner-Lambert Company, Morris Plains, NJ 07950

---

*In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

ANNALS OF SURGERY

Vol. 190 August 1979 No. 2

CONTENTS

129 **Pathologic Identification of Poor Prognosis Stage 1 ($T_1N_0M_0$) Cancer of the Breast**
Thomas F. Nealon, Jr., M.D., *Andrew Nkongho,* M.D., *Carlo Grossi,* M.D., *John Gillooley,* M.D., *New York, New York*

133 **Sex Hormone Binding Globulin as a Reliable Indicator of Hormone Dependence in Human Breast Cancer**
Yoichi Murayama, Joji Utsunomiya, Isamu Takahashi, Masatsugu Kitamura, Takeshi Tominaga, Tokyo, Japan

139 **Essential Fatty Acid Deficiency in Total Parenteral Nutrition: Detection by Changes In Intraocular Pressure**
Herbert Freund, M.D., *Nava Floman,* M.D., *Bernard Schwartz,* M.D., *Josef E. Fischer,* M.D., *Boston, Massachusetts*

144 **Effect of Protein Depletion and Repletion on Liver Structures, Nitrogen Content and Serum Proteins**
Janet Blanchard, M.D., *Ezra Steiger,* M.D., *Meagan O'Neil,* B.A., *Herbert Naito,* PH.D., *Bruce Sebeck,* M.D., *Raymond J. Shamberger,* PH.D., *Cleveland, Ohio*

151 **Carcinoma of the Hepatic Hilus: Surgical Management and the Case for Resection**
Bernard Launois, M.D., *Jean-Pierre Campion,* M.D., *Pierre Brissot,* M.D., *Michel Gosselin,* M.D., *Rennes, France*

158 **Risk Reduction in Gastric Operations for Obesity**
Edward E. Mason, M.D., *Kenneth J. Printen,* M.D., *Patricia Barron, Jeffrey W. Lewis,* M.D., *G. P. Kealey,* M.D., *Thomas J. Blommers,* PH.D., *Iowa City, Iowa*

166 **Stapled Cystogastrostomy: A Method of Treatment for Pediatric Pancreatic Pseudocyst**
F. Taghizadeh, M.D., *R. J. Bower,* M.D., *W. B. Kiesewetter,* M.D., *Pittsburgh, Pennsylvania*

170 **Evidence for a Pyloro-Cholecystic Reflex for Gallbladder Contraction**
H. T. Debas, M.D., *T. Yamagishi,* M.D., *Vancouver, B.C., Canada*

176 **Common Bile Duct and Oddi Sphincter Pressure Before and After Endoscopic Papillotomy in Patients with Common Bile Duct Stones**
P. Funch-Jensen, A. Csendes, M.D., *A. Kruse,* M.D., *M. J. Oster,* M.D., *E. Amdrup,* M.D., *Arhus, Denmark*

Now...enteral hyperalimentation by special delivery.

No pumps
Allows continuous gravity-flow administration.

Lightweight
Ambulatory patients can maneuver with more ease.

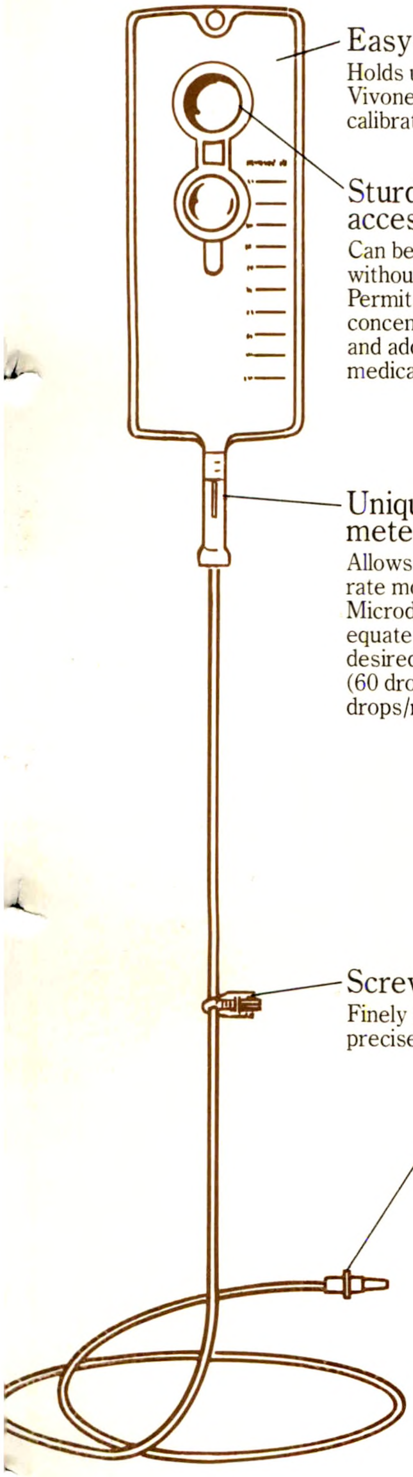
Eliminates jerry-rigging
A single component that's disposable. Saves time for the entire staff.

Economical
Just add Vivonex HN and a feeding tube

Simple flow regulation

"The plastic bag administration set and a microdrip chamber permit accurate administration during a wide range of rates. The elimination of the need for an infusion pump renders the technique less expensive and cumbersome. The patients may be fully ambulatory while receiving therapy."[1]

Special... because it's a complete system.



Easy-to-fill pouch
Holds up to 1 liter of Vivonex HN; 100-ml calibrations add accuracy.

Sturdy pouch access
Can be opened and closed without weakening. Permits volume or concentration changes and addition of vitamins or medications.

Unique drip meter
Allows simple flow-rate monitoring. Microdrops/minute equate to ml/hr for desired flow rate (60 drops≈1 ml; 60 drops/min≈60 ml/hr).

Screw clamp
Finely threaded for precise adjustment.

Male Luer
Fits most small-caliber feeding tubes.

References: 1. Page CP, Ryan JA Jr, Haff RC: Continual catheter administration of an elemental diet. *Surg Gynecol Obstet* 142:184-188, 1976. *2.* Randall HT (ed): Nutrition and surgical patients. *Contemp Surg* 11(1):7-22, 1977. *3.* Blackburn GL, Bistrian BR: Nutritional care of the injured and/or septic patient. *Surg Clin North Am* 56:1195-1224, 1976.

Special...because it delivers Vivonex® HN.*

VIVONEX HN provides complete enteral nutrition with free amino acids. Being truly elemental, it requires minimal digestion and allows maximal absorption. The extremely low viscosity allows Vivonex HN to flow continuously, at *any* rate, without clogging.

"Increasingly, these diets are used in patients with fistulas, inflammatory bowel disease, partial obstruction, and malabsorption—states for which total parenteral nutrition was once considered most appropriate."[2]

VIVONEX HN—*the only elemental high nitrogen diet*—has "...a nitrogen to calorie ratio of 1:150—the best ratio for anabolism."[3] By continuous administration of Vivonex HN via the Vivonex Delivery System, the same positive nitrogen balance, weight gain, and accelerated wound healing can be achieved as with parenteral hyperalimentation, but without the catheter-induced thrombophlebitis, sepsis, and patient discomfort.

*Information on Vivonex HN usage and precautions accompanies the product and should be reviewed before use.

Norwich-Eaton Pharmaceuticals
Division of Morton-Norwich Products, Inc.
Norwich, NY 13815

VIVONEX®

DELIVERY SYSTEM

EV-8061

CONTENTS *Continued*

179 **Primary Malignant Duodenal Tumors**
Raymond P. Kerremans, M.D., *Jan Lerut,* M.D., *Freddy M. Penninckx,* M.D., *Leuven, Belgium*

183 **Major Complications of Small Bowel Diverticula**
John W. Donald, M.D., *Mobile, Alabama*

189 **Review of 404 Patients with Gastrointestinal Fistulas: Impact of Parenteral Nutrition**
Peter B. Soeters, Amin M. Ebeid, Josef E. Fischer, M.D., *Boston, Massachusetts*

203 **Role of Arteriography in Rectal Hemorrhage Due to Arteriovenous Malformations and Diverticulosis**
E. Armistead Talman, M.D., *Dirk S. Dixon,* M.D., *Fabio E. Gutierrez,* M.D., *Richmond, Virginia*

214 **A Long-term Follow-up of Patients Resected for Benign Esophageal Stricture Using the Inkwell Esophagogastrostomy**
P. Wara, M. J. Oster, P. Funch-Jensen, J. Andresen, P. Ottosen, Arhus, Denmark

218 **The Role of Cardiovascular Hemodynamics and Liver Histology in Evaluating Bleeding Cirrhotic Patients**
V. DiCarlo, C. Staudacher, R. Chiesa, B. Andreoni, M. Cristallo, E. Ronchetti, Milan, Italy

227 **Intravascular Coagulation and Fibrinolysis within Primate Extremities During Tourniquet Ischemia**
Stephen H. Miller, M.D., *M. Elaine Eyster,* M.D., *Abdus Saleem,* M.D., *Larry Gottleib,* M.D., *David Buck,* M.S., *William P. Graham, III,* M.D., *Hershey, Pennsylvania*

231 **A Method for Primary Reconstruction Following Radical Excision of Sacrococcygeal Pilonidal Disease**
Ronald H. Fishbein, Jacob C. Handelsman, Baltimore, Maryland

236 **Effects of Methylprednisolone on Experimental Pulmonary Injury**
F. W. Cheney, Jr., M.D., *T. H. Huang,* M.D., *R. Gronka,* B.S., *Seattle, Washington*

243 **Revascularization of the Ischemic Canine Hindlimb by Arteriovenous Reversal**
Kaj Johansen, M.D., *Eugene F. Bernstein,* M.D., *La Jolla, California*

254 **Minor Hemobilia: Clinical Significance and Pathophysiological Background**
Philip Sandblom, M.D., *Velimir Mirkovitch,* M.D., *Lausanne, Switzerland*

Notice to Contributors and Subscribers

ANNALS OF SURGERY is a monthly journal which considers for publication original articles in the field of surgery. It is the oldest continuously published journal in the English language solely devoted to the surgical sciences. The Editorial Board considers only papers judged to offer significant contributions to the advancement of surgical knowledge.

CONTRIBUTIONS. Four typed copies of the manuscript and four copies of the illustrations should be sent prepaid to the Chairman of the Editorial Board of ANNALS OF SURGERY:

David C. Sabiston, Jr., M.D.
Annals of Surgery
Department of Surgery
Duke University Medical Center
Durham, North Carolina 27710

Manuscripts and references should be typed double spaced on one side of 8½ × 11 paper leaving wide margins. Authors should retain a complete copy of the manuscript including illustrations in the event that the manuscripts are lost in the mail. A complete address for reprint requests should be included on the title page together with the name of the institution from which the work is being published.

An abstract of *not more than 200 words* should be placed at the beginning of the manuscript. It should accurately reflect the paper and provide readers with a reliable impression of the contents and conclusions of the work.

Digits one to ten should be spelled out, except when used for units of measurement (time, weight, volume, dosage, degrees) percentage, or when decimals are involved; for numbers above ten, numerals should be used. Dorland's Medical Dictionary and Webster's International Dictionary may be used as standard references. Scientific names for drugs should be used when possible. Copyright or trade names of drugs should be capitalized. Units of measurement should be expressed in the metric system. Temperature should be expressed in degrees centigrade. All contributions should be submitted in English.

Black and white illustrations will be reproduced free of charge, but the publisher reserves the right to establish a reasonable limit upon the number supplied. Color illustrations will be published at the author's expense. Black and white photographs should be in the form of glossy prints. Line and wash drawings should be black on white paper, with lettering in black india ink or transfer lettering, large enough to be readable after necessary reduction. Large or bulky illustrations should be accompanied by smaller glossy reproductions of the same. Illustrations should be numbered, the tops indicated, and the author's name and the title of the article in brief appear on the back. A separate typewritten sheet of legends for the illustrations should be supplied.

An alphabetical list of numbered references should appear at the end of the manuscript with corresponding numbers in the text. All references should be specifically mentioned in the body of the manuscript. The list of references should be *selective* with not more than 20 references except under unusual circumstances. References should conform to the style of the Index Medicus.

McNamara, J. J., Molot, M. D. and Stremple, J.: Changes in Some Physical Properties of Stored Blood. Ann. Surg., 174:58, 1971.

PUBLISHER'S NOTICES

CHANGE OF ADDRESS: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the journal.

Copies will not be replaced without charge unless we receive a request within 60 days of the mailing in the U. S. or within 90 days in all other countries.

BUSINESS ADDRESS: Subscriptions, reprints, advertising, and all business communications should be addressed to:

ANNALS OF SURGERY
J. B. Lippincott Co.
East Washington Square
Philadelphia, Pa. 19105

Published Monthly. Subscription Rates $27.00 per year in United States and possessions; all other countries $37.00. All prices include postage. Single issues $5.00. Rate foı Residents, U.S. only, $19.00.

The publishers accept no responsibility for opinions expressed by contributors.

Develop a Positive from a Negative.

Trauma, sepsis, injury, and disease are all catabolic processes that can deplete the body's nitrogen reserves. Aggressive nutritional support should be provided to restore a positive nitrogen balance.

Nitrogen Balance

Deca-Durabolin is a powerful anabolic steroid which promotes tissue-building processes and reverses catabolism. Used as an adjunct to other modes of nutritional therapy, Deca-Durabolin may help to develop a positive nitrogen balance. Its high anabolic/androgenic ratio allows the employment of doses that provide significant anabolic effects with reduced risk of androgenic effects.

Deca-Durabolin®

nandrolone decanoate injection, NF

BRIEF SUMMARY: Please consult full product information in the package insert before prescribing.

> NAS/NRC review panels have classified Deca-Durabolin possibly effective in the treatment of those conditions in which a potent tissue-building or protein-sparing action is desired (e.g. pre and post surgical care, burns).

CONTRAINDICATIONS:
1. Male patients with carcinoma of the prostate or breast. **2.** Carcinoma of the breast in some females. **3.** Pregnancy, because of masculinization of the fetus. **4.** Nephrosis or the nephrotic phase of nephritis.

WARNING: Anabolic steroids do not enhance athletic ability.

PRECAUTIONS:
1. Hypercalcemia may develop both spontaneously and as a result of hormonal therapy in women with disseminated breast carcinoma. If it develops while on this agent, the drug should be stopped. **2.** Caution is required in administering these agents to patients with cardiac, renal or hepatic disease. Edema may occur occasionally. Concomitant administration with adrenal steroids or ACTH may add to the edema. **3.** If amenorrhea or menstrual irregularities develop the drug should be discontinued until the etiology is determined. **4.** Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain the prothrombin time at the desired therapeutic level. **5.** Anabolic steroids have been shown to alter glucose tolerance tests. Diabetics should be followed carefully and the insulin or oral hypoglycemic dosage adjusted accordingly. **6.** Anabolic steroids should be used with caution in patients with benign prostatic hypertrophy. **7.** Serum cholesterol may increase during therapy. Therefore, caution is required in administering these agents to patients with a history of myocardial infarction or coronary artery disease. Serial determinations of serum cholesterol should be made and therapy adjusted accordingly.

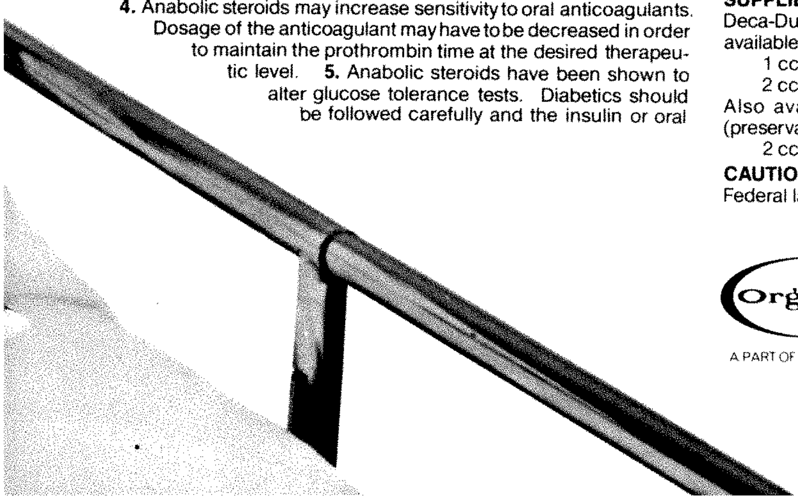
ADVERSE REACTIONS:
1. In Males: a. Prepubertal: 1) Phallic enlargement, 2) Increased frequency of erections, b. Post-pubertal: 1) Inhibition of testicular function and oligospermia, 2) Gynecomastia. **2.** In Females: a. Hirsutism, male pattern baldness, deepening of the voice and clitoral enlargement. These changes are usually irreversible even after prompt discontinuance of therapy and are not prevented by concomitant use of estrogens, b. Menstrual irregularities, c. Masculinization of the fetus. **3.** In Both Sexes: a. Nausea, b. Increased or decreased libido, c. Acne (especially in females and prepubertal males), d. Inhibition of gonadotropin secretion, e. Bleeding in patients on concomitant anticoagulant therapy, f. Premature closure of epiphyses in children. **4.** Alterations in these clinical laboratory tests: a. The metyrapone test, b. Glucose tolerance test, c. The thyroid function tests: a decrease in the PBI, in thyroxine-binding capacity and radioactive iodine uptake, d. The electrolytes: retention of sodium, chlorides, water, potassium, phosphates and calcium, e. Liver function tests: 1) Increased serum cholesterol, 2) Suppression of clotting factors II, V, VII, and X. **5.** There have been rare reports of hepatocellular neoplasms and peliosis hepatis in association with long-term androgenic-anabolic steroid therapy.

SUPPLIED:
Deca-Durabolin (in sterile sesame oil solution for intramuscular injection) is available in a potency of 50 mg./cc. with 10% benzyl alcohol (preservative):
1 cc. ampuls, box of 4. NDC #0052-0696-14
2 cc. multiple dose vial. NDC #0052-0696-02
Also available in a potency of 100 mg./cc. with 10% benzyl alcohol (preservative):
2 cc. multiple dose vial. NDC #0052-0697-02

CAUTION:
Federal law prohibits dispensing without prescription.

Organon
A PART OF Akzona INC.

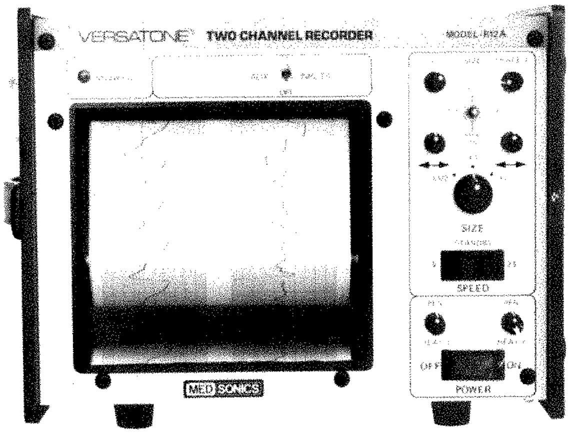
Organon Pharmaceuticals
A Division of Organon Inc.
West Orange, N.J. 07052



VERSATILE INSTRUMENTS FOR THE VASCULAR LABORATORY

VERSATONE® BI-DIRECTIONAL DOPPLER MODEL D9 Used with one of four plug-in probes, MedaSonics Bi-directional Doppler employs ultrasound and the Doppler shift principle to detect blood flow and to distinguish the direction of flow. It provides explicit separation of advancing and receding blood flow, even in the presence of simultaneous flow in two directions. The Model D9 has a variety of outputs, including built-in loudspeaker, stereo headphones, tape recorder jacks, and calibrated outputs for graphic recording. Three pencil type probes (5MHz, 8MHz and 10MHz) and one flat probe (5MHz) suitable for taping in place are available.

VERSATONE® BI-DIRECTIONAL DOPPLER
VERSATONE® TWO CHANNEL RECORDER
MEDSONICS



VERSATONE TWO-CHANNEL CHART RECORDER MODEL R12A The VERSATONE two-channel Chart Recorder is used to chart the Doppler signals of forward and reverse blood flow from the Model D9 Bi-directional Doppler. This Recorder can also chart an ECG signal, by itself or mixed with a Doppler signal. An optional, built-in ECG preamp is available. In addition, the R12A accepts many other "high level" physiologic signals you may wish to record, including those obtained from MedaSonics PPG equipment.

PHOTOPULSE® PPG SENSORS AND MODEL PA13 ADAPTOR The PHOTOPULSE photoplethysmograph (PPG) provides a sensitive means of detecting blood volume changes in the microcirculation close to the skin's surface. It may be applied to those parts of the body with good capillary beds, including digital pads, where it can be used to monitor pulse. The PPG also is used in a non-invasive procedure to detect significant obstruction of the extracranial internal carotid artery. Two PHOTOPULSE sensors are placed under a head band over each supraorbital area to record volume changes that occur when a series of compression maneuvers are carried out.

The PA13 adaptor allows the use of two PPG sensors with the R12A recorder or with other laboratory chart recorders.

For more information on these and other instruments for the vascular laboratory, call or write:

MEDASONICS

Dept. AS • 340 Pioneer Way, P.O. Box M • Mountain View, CA 94042
Toll-free telephone 800 227-8076 • In California, call collect (415) 965-3333
Telex: 33-4448 • Cable: MEDASONICS

ANNALS OF SURGERY

Vol. 190 August 1979 No. 2

Pathologic Identification of Poor Prognosis Stage I ($T_1N_0M_0$) Cancer of the Breast

THOMAS F. NEALON, JR., M.D., ANDREW NKONGHO, M.D., CARLO GROSSI, M.D., JOHN GILLOOLEY, M.D.

From the Departments of Surgery and Pathology, St. Vincent's Hospital and Medical Center of New York and the Department of Surgery, New York University School of Medicine, New York, New York

Twenty to 40% of Stage I($T_1N_0M_0$) cancers of the breast recur in ten years. This is an attempt to identify those patients in whom the disease is likely to recur. On the basis of a study of the histologic changes in the tumor and treatment failures poor prognosis was associated with several histological characteristics: poor cytologic differentiation; lymphatic permeation; blood vessel invasion and invasion of the tumor into the surrounding soft tissue. This classification was then applied to 363 cancers of the breast seen over a five year period and followed three to eight years. There were 203 Stage I ($T_1N_0M_0$) tumors in the group. Ninety-four of the 203 Stage I tumors had one to four of the above histologic characteristics; 109 had none. Among the 109 patients characterized as good risks there were two treatment failures (2%). In the group of 94 with any high risk histologic features there were 47 treatment failures (50%) which were statistically significant ($p = 0.001$). The histologic changes had a cumulative effect on the degree of malignancy of the tumor. Pathologic changes in the tumor identified those patients whose Stage I ($T_1N_0M_0$) tumors were likely to recur.

The best results in the treatment of invasive cancer of the breast have been obtained in those patients with lesions smaller than 2 cm in diameter whose cells have not yet spread to the regional lymph nodes ($T_1N_0M_0$). However, the ten year survival of such patients is only 60–80%.[1,3] Identification of the patients whose disease is likely to recur would isolate those who require more or different treatment. This report details identification of this group on the basis of pathologic evaluation of the tumor.

At the time of their original treatment we noted several Stage I ($T_1N_0M_0$) breast cancers in patients whose tumors had histologic characteristics suggestive of high malignant activity. When these patients did poorly over a period of a few years, it was decided to review such cases and correlate the microscopic picture with the long-term course of the patients.

The original pathology reports of all patients who had definitive surgical treatment for primary breast cancer at St. Vincent's Hospital from January 1, 1971 through December 31, 1975 were reviewed. Excluded were bilateral simultaneous breast cancers (3 patients), second primary breast cancers (6 patients) and males (2 patients). There were 363 patients in the group. Among those there were 203 patients whose cancer grossly was less than 2 cm in diameter and had not spread to the axillary lymph nodes on histologic examination ($T_1N_0M_0$). The original pathology reports of these patients were reviewed. Particular attention was directed to age, size of the tumor, presence of disease in lymph nodes, histologic type, degree of differentiation, cell reaction to the tumor, vascular invasion, lymphatic permeation, skin or nipple involvement, perineural spread, infiltration into the soft tissues and tumor necrosis. Our Cancer Registry maintained follow-up information on these patients including any additional treatment and results. The results of their follow-up were correlated with the pathologic analysis. Three patients were lost to follow-up. Poor prognosis was associated with a combination of several patho-

---

Reprint requests to: Thomas F. Nealon, Jr., M.D., 170 West 12 Street, New York, NY 10011.

Supported in part by a grant from the John V. Mara Fund.

Submitted for publication: January 2, 1979.

0003-4932/79/0800/0129 $00.70 © J. B. Lippincott Company

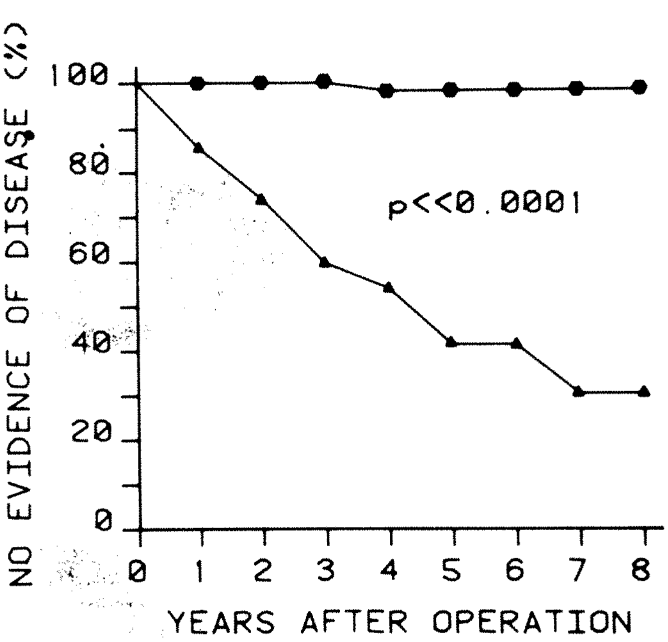


FIG. 1. Graphic presentation of the influence of histologic markers on disease-free interval in 203 patients with $T_1N_0M_0$ breast cancer. Risk criteria on the presence of 1 to 4 markers. There is a high statistical significance. ●—● 109 patients not meeting risk criteria. ▲—▲ 94 patients meeting risk criteria.

logic characteristics—poor cytologic differentiation, lymphatic permeation, blood vessel invasion and invasion of the tumor into the surrounding tissues.

Tumors were designated high grade (poor cytologic differentiation) when they possessed certain characteristics: 1) variation in nuclear size and chromatin clumping, 2) high rate of mitotic activity, 3) irregular nuclear membranes and 4) a single cell pattern of invasion (except in cases of lobular carcinoma).

The presence of nests of tumor cells within lymphatic spaces was required for our diagnosis of lymphatic permeation.

Tumor thrombi within the lumen or invasion of the walls of blood vessels by malignant cells were categorized as vascular invasion.

Although most carcinomas of the breast invade the surrounding tissue to some extent, some types are more apt to be circumscribed than others. We categorized the tumors as poorly circumscribed when there was an irregular pattern of invasion of the carcinoma into adjacent tissues. The evaluation was based on the gross and microscopic appearances of the tumor.

Results

The 203 ($T_1N_0M_0$) tumors were comprised of 35 high grade adenocarcinomas, 153 moderately differentiated adenocarcinomas, six medullary, four mucinous and five lobular carcinomas. Two sarcomas were excluded from the study.

Ninety-four of the 203 tumors had one to four of the above histologic characteristics; 109 had none. Among the 109 patients who were categorized as good risks, there were two treatment failures (2%). In the group of 94 patients with any high risk histologic characteristics there were 47 treatment failures (50%) (Fig. 1).

The most common histologic characteristic was lymphatic permeation which was present in 73 tumors (36%). Blood vessel invasion found in 40 tumors (20%), was never found as an isolated characteristic and occurred only in combination with one or more of the other characteristics in the more malignant tumors. Poor circumscription occurred in 39 tumors (19%). Thirty-five tumors (17%) were of the high grade varieties (poor cytologic differentiation). These were evenly divided through all groups with nine occurring in both the highly malignant four characteristic group and in the less aggressive one characteristic group.

Curves of "no evidence of disease" status were calculated using actuarial methods designed for the analysis of occurrence of nonfatal events.[2] The possibility that the difference between any two curves was due to chance (null-hypothesis) was tested by the chi-square method.

We have a sample of 203 patients treated for Stage I carcinoma of the breast. They are divided into two groups according to their meeting or not meeting a set of criteria of risk established by the investigators and analyzed according to their suffering or not suffering failure (Table 1): Group I consists of 109 patients who did not meet the criteria of risk and Group II consists of 94 patients who met the criteria of risk. Two of the 109 patients in Group I (did not meet criteria of risk) suffered treatment failure whereas 47 of the 94 patients in Group II (met criteria of risk) suffered treatment failure.

Treatment failure occurred in all patients when all four histologic changes were present. The tumors in the nine patients in this group recurred an average of 12 months after operation and most died shortly thereafter (Fig. 2). Many of these patients had micro-

TABLE 1. *Contingency Table*

Groups	Variable 1 (Treatment Failure)	Variable 2
Group I (did not meet criteria) 109 patients	2	107
Group II (met criteria) 94 patients	47	47

X^2 (one degree of freedom) = 63.9, $p \ll 0.0001$. There is a very highly significant statistical difference between Groups I and II.

scopic involvement of the skin which was not evident grossly.

When three histologic changes were present, the results were only slightly better (Fig. 2). Treatment failure occurred in 15 of the 20 patients (75%) in this group an average of 26 months after operation with substantially longer survival rates. There was a significant difference in treatment failure when compared to the group with four histologic changes (Fig. 2).

The results were similar when only two histologic changes were present (Fig. 2). Sixteen failures occurred in the 26 patients (60%) an average of 28 months after operation. There was no significant difference in treatment failure when compared to the group with three histologic changes.

The tumors with only one change present were less aggressive (Fig. 2). Eight treatment failures occurred among the 39 patients (20%). They appeared an average of 41 months after operation. It is quite possible more will occur with a longer follow-up. No single marker predominated among the recurrences in this group which were divided between poor cytologic differentiation, lymphatic permeation and soft tissue invasion. There was a significant difference between the treatment failures in this group and the group with two histologic changes (Fig. 2).

It appeared that treatment failure was influenced by adjuvant therapy. To better measure the effect of surgical treatment on those tumors with histologic changes, the patients who also received some form of adjuvant treatment were eliminated from the group and restudied.

Among those patients treated surgically 32 of the 34 (94%) patients with four, three or two markers had treatment failure an average of seven, 18 and 25 months after operation.

In this study, pathologic changes were an effective means of earmarking those tumors which were likely to recur. Studies are in progress which will better delineate the effect of treatment on both treatment failure and survival.

We reviewed the histologic picture and the clinical course of larger lesions which had not metastasized ($T_2N_0M_0$) and ($T_3N_0M_0$). While histologic changes were present in most cases, they did not correlate with the clinical course of the ($T_2N_0M_0$) and ($T_3N_0M_0$) lesions as well as they did with the course of the ($T_1N_0M_0$) tumors. Treatment failure occurred more commonly in larger lesions even when they showed none of the histologic changes. The changes were best able to separate the bad prognosis lesions at the $T_1N_0M_0$ level.

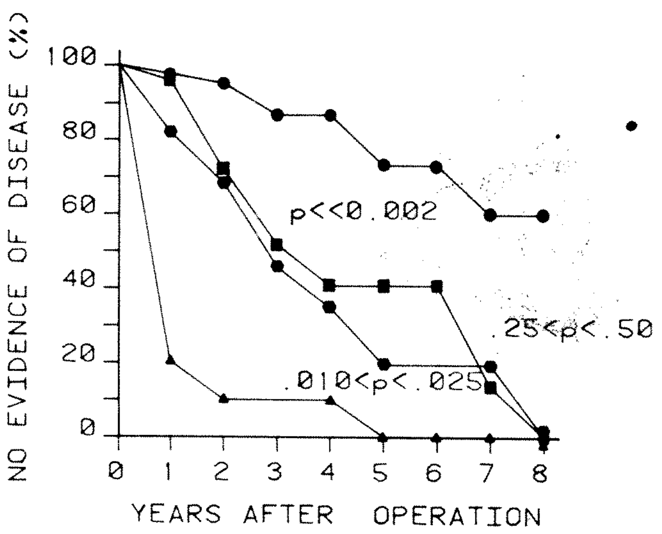


FIG. 2. Carcinoma of the breast ($T_1N_0M_0$) in 94 patients meeting risk criteria to various extents. Graphic presentation of the cumulative influence of the histologic markers on disease free interval. + denotes a single histologic marker. The p probability is statistically significant between the curve of + and those of ++ and +++. It is not significant between the curves of ++ and +++ and again is significant between the curves of ++ and +++ and the curve of ++++. ●+ (39 patients) ■++ (26 patients) ⬢ +++ (20 patients) ▲++++ (9 patients).

The average age of the 109 patients without pathologic changes was 68 years. Twenty-four of the 109 patients were under 50 years old. The average age of the 94 patients with one to four histologic changes was 61. Twenty-seven of the 94 patients were under 50 years old. Sixteen failures occurred in the 27 patients under 50 years of age with histologic changes (60%) while the other 28 failures occurred in the 67 patients over 50 whose tumors had histologic changes (42%). These figures are not statistically significant.

Discussion

Surgeons have been concerned for many years because 20–40% of what they considered good risk patients eventually become treatment failures within 10 years.[9,10] As long as there was no way to separate the potential problems, any prospective studies would have to be applied to all the cases, making an unrealistically large sample necessary.

Delineation of the high risk group will make prospective studies on this group possible, hopefully with good results. Concern with this ill-fated group in a Stage I category has interested many investigators recently. The concept that these patients have been categorized $T_1N_0M_0$ when many may have undetected micrometastases has been broached and, in at least three studies, documented.

In 1948 Saphir and Amromin[13] restudied the axillary nodes in 30 patients in whom routine processing failed to disclose metastases and found tumor in ten patients by examining alternate serial sections. Some of these were micrometastases.

Pickren, in 1961,[12] in a similar study of 51 patients found tumors in 22% of the patients previously considered negative. Fisher, et al.[6] found occult metastases in 24% of the lymph nodes which after "routine" pathological examination were regarded as negative for metastases in 78 $T_1N_0M_0$ cases.

In none of the three studies were researchers able to correlate their findings with any change in prognosis. It is of interest that 24% of the patients studied died of their disease or are living with recurrence regardless of the presence of occult metastases.

None of Fisher's patients whose occult metastases manifested as tumor emboli in capsular lymphatics died from their disease. On the other hand, five of the patients with lesions that presented as "true" metastases in the substance of the nodes died of the disease five years later. Yet four with such metastases were free of disease five years later. We have done no studies on micrometastases and are unable to contribute to this point.

All of the characteristics used in our categorization have been considered significant by various authors. Fisher[5,7] mentioned all of these characteristics in the 16 histopathologic characteristics with which they correlated the presence or absence of occult metastasis. The Memorial group[3] considered lymphatic invasion of some, but limited, significance. However, no one considered the histologic changes as having a cumulative effect. Nime, et al.[11] found the incidence of distant metastases significantly greater in patients designated as having Stage I disease after routine pathologic study who exhibited intralymphatic tumor emboli as opposed to those (matched controls) who did not. Bonadonna[4] also regarded this as an important prognostic discriminant in breast cancer since detection of such emboli would warrant the use of chemotherapy in those patients who might not otherwise receive such adjunctive therapy.

The experiences of Fisher and Bonadonna would suggest chemotherapy as the most desirable adjuvant. On the other hand, if one subscribes to the study of Huvos, et al.,[18] who demonstrated a step-like progression up the axilla, radiotherapy might be the preferable treatment. Now that we have learned to categorize the poor risk Stage I lesions, we are retrospectively reviewing our experience with the specific purpose of weighing the impact of the various types of operations and adjuvant therapy on the course of those tumors with unfavorable histologic changes.

Fisher found age to be the only good correlation with prognosis in the National Surgical Adjuvant Breast Program (NSABP) patients. Age did not correlate with prognosis as well as the histologic changes in our patients.

The current study allows a three to eight year follow-up. Since a large percentage of the treatment failures occur before 30 months, follow-up of as little as three years was included even though more failures will occur. The present method of reporting on the specimens was adopted in 1971 by our Pathology Department in conformity with the standards established by the NSABP. These reports detail all the data necessary for histologic classification. We elected to restrict this initial report to those tumors where the interpretation was made at the time of operation and no prejudice as to long-term clinical response was possible.

This type of categorization is widely available. It can be carried out by a competent Pathologist in any hospital laboratory with the equipment currently on hand.

References

1. Adair, F., Berg, J., Jonbert, L. and Robbins, G. F.: Long Term Followup of Breast Cancer Patients: One 30 Year Report. Cancer, 33:1145, 1974.
2. Anderson, R. P., Boncheck, L. I., Grunkemeier, G. L., et al.: The Analysis and Presentation of Surgical Results by Actuarial Methods. J. Surg. Res., 16:224, 1974.
3. Berg, J. and Robbins, G. F.: Factors Influencing Short and Long Term Survival of Breast Cancer Patients. Surg. Gynecol. Obstet., 122:1311, 1966.
4. Bonadonna, G.: A New Prognostic Factor in Breast Cancer. Am. J. Surg. Pathol. 1:73, 1977.
5. Fisher, E. R., Gregorio, R. M. and Fisher, B.: The Pathology of Invasive Breast Cancer. A Syllabus Derived from the Findings of the National Surgical Adjuvant Breast Project (Protocol #4) Cancer, 36:1, 1975.
6. Fisher, E. R., Swanidoro, S., Lee, C. H., et al.: Detection and Significance of Occult Axillary Node Metastases in Patients with Invasive Breast Cancer. Cancer, 42:2025, 1978.
7. Fisher, E. R., Polekar, A., Rockette, H., et al.: Pathologic Findings from the National Surgical Adjuvant Breast Project (Protocol #4) Cancer, 42:2032, 1978.
8. Huvos, A. G., Hutter, R. V. P. and Berg, J. W.: Significance of Axillary Macrometastasis & Micrometastases in Mammary Cancer: Ann. Surg., 173:44, 1971.
9. Malinin, T. and Lumb, G.: Survival of Patients with Carcinoma of Breast Without Lymph Node Metastasis in Relation to the Tumor Types. J. Surg. Oncol. 9:221, 1977.
10. Moore, F. D.: The Breast p. 265 in Management of Patient with Cancer, Nealon, T. F. Jr., Second edition. Philadelphia, W. B. Saunders. 1976. (ed).
11. Nime, F. A., Rosen, P., Thaler, H., et al.: Prognostic Significance of Tumor Emboli in Intramammary Lymphatics in Patients with Mammary Carcinoma. Am. J. Surg. Pathol. I, No. 1 March 1977. p. 25.
12. Pickren, J. W.: Significance of Occult Metastases. A Study of Breast Cancer. Cancer, 14: 1266, 1961.
13. Saphir, O. and Amromin, E. D.: Obscure Axillary Lymph Node Metastases in Carcinoma of the Breast. Cancer, 1: 233, 1948.

Sex Hormone Binding Globulin as a Reliable Indicator of Hormone Dependence in Human Breast Cancer

YOICHI MURAYAMA, JOJI UTSUNOMIYA, ISAMU TAKAHASHI,* MASATSUGU KITAMURA,*
TAKESHI TOMINAGA*

From the Second Department of Surgery, Tokyo Medical and Dental University, Tokyo, Japan

One hundred nine pre- and postmenopausal mammary carcinoma cases were studied to elucidate the role of sex hormone binding globulin (SHBG) in the hormone dependence of human breast cancer. Our findings indicate that there is a significant negative correlation between SHBG binding capacity and plasma testosterone concentration. All patients with high SHBG titers were found to be cytosol estrogen receptor (CER) positive and the plasma SHBG binding capacity of CER positive was significantly higher than that of CER negative patients. We also found that the level of pretherapy plasma SHBG concentration is a reliable indicator in predicting the efficacy of hormone therapy. Our findings also confirm that, for a tumor to be hormone dependent, high plasma SHBG concentration and estrogen receptors must be present simultaneously. The present pretherapy determination of SHBG titers is easier and more reliable than previous methods for determining the hormone dependence of human breast tumors.

SEX HORMONE BINDING GLOBULIN (SHBG) is the specific binding protein which has been suggested to regulate the biological activity of sex steroids in the blood.[5] In normal subjects, SHBG is increased by an increase in endogenous estrogen[5,6,27] and decreased by an increase in endogenous testosterone.[1,5,12,20] The change in SHBG during the menstrual cycle is much smaller than the radioimmunoassay-determined change of plasma estradiol or plasma testosterone.[27] In breast cancer patients, the administration of exogenous sex steroids effects a change in the binding capacity of SHBG[6] and after oophorectomy or adrenalectomy, SHBG decreases to the level of one-half or one-third of that before hormone therapy.

McGuire, et al.[14] reported that the presence of receptors in breast tumors is one of the reliable indicators for their hormone dependence. However, not all receptor-positive tumors respond to endocrine therapy and only 60–65% of those tumors regress. Experimental and clinical studies revealed a change in the estrogen receptor level which was associated with a change in the levels of endogenous steroid hormones such as estrogen and progesterone.[2,4,8,9,15–17]

These findings suggest that the hormone dependence of breast tumors is subject to two factors—the presence of receptors and the endogenous hormone environment which reacts to the receptor system. We hypothesized that a specific endogenous hormone environment which shows an increase in SHBG initiates and promotes estrogen receptor synthesis in human breast tumors and that hormone-dependent breast cancer evidences an increase in SHBG and estrogen receptors. To test this hypothesis, we examined the relationship between SHBG binding capacity and endogenous testosterone concentration, analyzed the relationship between SHBG binding capacity and the presence of cytosol estrogen receptors (CER) and determined the reliability of SHBG binding capacity prior to hormone therapy as an indicator of the hormone dependence of the breast tumor.

Materials and Methods

Subjects

The 109 patients were divided into three groups. None of the patients or controls were pregnant, had endocrine disease, or were receiving medication, and all had normal liver and thyroid functions. With the exception of three patients in Group C, none of the patients had undergone prior hormone therapy.

In Group A (24 patients), the relationship between plasma testosterone concentration and SHBG binding

---

* Tokyo Metropolitan Komagome Hospital, Tokyo, Japan.

Reprint requests: Yoichi Murayama, The Second Department of Surgery, Tokyo Medical and Dental University, Tokyo 113, Japan.

Supported in part by a research grant (51-7) from the Intractable Disease Division, Public Health Bureau, Ministry of Health and Welfare, Japan.

Presented in part at the XII International Cancer Congress.

Submitted for publication: November 14, 1978.

0003-4932/79/0800/0133 $00.80 © J. B. Lippincott Company

capacity was assayed simultaneously. This group consisted of 13 pre- and 11 postmenopausal primary breast cancer patients ranging in age from 25 to 74 years (average 47).

In Group B (35 patients), the relationship between plasma SHBG binding capacity and CER was examined. This group consisted of 13 pre- and 22 postmenopausal primary breast cancer patients ranging in age from 29 to 73 years (average 52). There were no distant metastases.

In Group C (50 patients), we assayed plasma SHBG concentration prior to therapy in order to determine whether pretherapy SHBG titers represent a reliable indicator for predicting the efficacy of hormone therapy. This group consisted of 17 pre- and 33 postmenopausal advanced breast cancer patients ranging in age from 33 to 72 years (average 54). These patients presented with metastatic breast cancer. Main metastatic lesions were found in soft tissues such as skin and lymph nodes of six pre- and 12 postmenopausal patients, in bone tissue of five pre- and ten postmenopausal patients, and in the lungs, pleura, liver, or brain of six pre- and 11 postmenopausal patients.

Determination of Plasma Testosterone Concentration (Group A)

Plasma testosterone concentration was determined by radioimmunoassay.[13] Testosterone-3-oxime-BSA which was used as antigen was produced by the method of Erlanger.[7] Testosterone-1β,2β-^{3}H (SA: 47 Ci/mmol) was obtained from the Radiochemical Center (Tokyo). Emulsion was prepared from 1 mg testosterone-3-oxime-BSA, 0.5 ml complete Freund's adjuvant and 0.5 ml normal saline. The antiserum was generated against testosterone-3-oxime-BSA, diluted according to the method of Furuyama,[10] and cross-reacted with the following steroids. The per cents of cross-reactivity with 5α-dihydrotestosterone, epitestosterone and androst-4-ene-3β,17β-diol were 118%, 47% and 26%, respectively. Separation and purification procedures were performed by the method of Wu[26] and cross-reaction was negligible. Separation of bound and free hormones was performed by 50% $(NH_4)_2SO_4$. The intra- and interassay variances were 10.2% and 11%, respectively. The least detectable concentration was 20 pg. The recovery rate and water blank were 85.8 ± 11%, and 7.46 ± 2.8 pg, respectively.

Determination of SHBG Binding Capacity (Group B)

SHBG binding capacity was determined by agar-gel electrophoresis with dextran-coated charcoal treatment.[19] One hundred microliters of serum and 1.5 nmol of [^{3}H]17-β-estradiol were incubated at 0–2° for two hours to obtain SHBG-17β-estradiol complex.

The free and loosely bound [^{3}H]17β-estradiol was then removed by the addition of 3 ml of ice cold dextran-coated charcoal suspension. Separation and purification was performed by agar-gel electrophoresis at a low temperature[24] and the radioactivity of each fraction was counted on a liquid scintillation counter (Packard).

Determination of CER (Group B)

CER was determined by the method of Wagner and Jungblut.[25]

Two hundred fifty milligrams of frozen tissue stored at −80° was ground with an autopulverizer in liquid nitrogen and homogenized with a Teflon® glass homogenizer in ice cold 0.01 M Tris HCl buffer (pH 7.4) into a volume four times that of the original tissue volume. The homogenate was centrifuged in a cooled centrifugal butylate tube at 130,580 × g at 4° for 30 minutes to obtain cytosol fractions as the supernatant. Tritiated 17β-estradiol (0.4 nmol) was incubated with 60 μl of cytosol at 0–2° for two hours to obtain 17β-estradiol receptor complex. The free and loosely bound tritiated 17β-estradiol was then removed by adding 0.5 ml ice cold dextran-coated charcoal suspension. Separation and purification was performed by agar-gel electrophoresis at low temperature.[24] After the agar-layer was fractionated into 3 mm widths, the radioactivity of each fraction was determined with a liquid scintillation counter (Packard).

Radioactivity Measurement

Plasma and cytosol samples in 3 mm sections of agar-gel were dissolved overnight in 5 ml Soluene and counted in 10 ml Instagel in a liquid scintillation counter (Packard) with a counting efficiency of 35%.

Hormone Therapy (Group C)

In premenopausal metastatic breast cancer patients (Group C), adrenalectomy, ovariotomy or androgen therapy were chosen. Adrenalectomy, including the resection of both ovaries, was performed in a one-step procedure via an upper abdominal incision. In three patients who had previously undergone ovariectomy for the treatment of advanced breast cancer, only the adrenal glands were removed. A maintenance dose of 50 mg cortisol/day was administered to patients postoperatively. Androgen therapy consisted of 30 mg testosterone/day for at least 30 days or until new lesions appeared or existing lesions increased by at least 25% above their smallest size recorded.[11]

The treatment for postmenopausal patients consisted of adrenalectomy, androgen or estrogen therapy. If menstruation had ceased less than five years previously, androgen therapy (30 mg testosterone/day for at least 30 days or until new lesions appeared or existing lesions increased by at least 25% above their smallest size recorded[11]) was instituted, if more than five years had elapsed since the patient's last menstrual period, estrogen therapy (15 mg diethylstilbestrol/day for at least 30 days or until new lesions appeared or existing lesions increased by at least 25% above their smallest size recorded[11]) was chosen.

All patients were closely observed for at least four weeks following initiation of the chosen treatment to determine its effectiveness.

Assessment of Therapy Response

Therapy response was evaluated according to the criteria of the International Union Against Cancer.[11] Objective remission was considered to have occurred if tumor size decreased by at least 50%, this decrease lasted for at least one month, other lesions remained unchanged, or no new lesions appeared.

Results

Relationship Between SHBG and Plasma Testosterone Concentration (Group A)

A significant negative correlation was noted between plasma testosterone concentration and SHBG binding capacity in the premenopausal patients of Group A (Fig. 1A).

In the postmenopausal patients, an inverse correlation between SHBG binding capacity and plasma testosterone concentration was noted. However, this correlation was not significant (Fig. 1B).

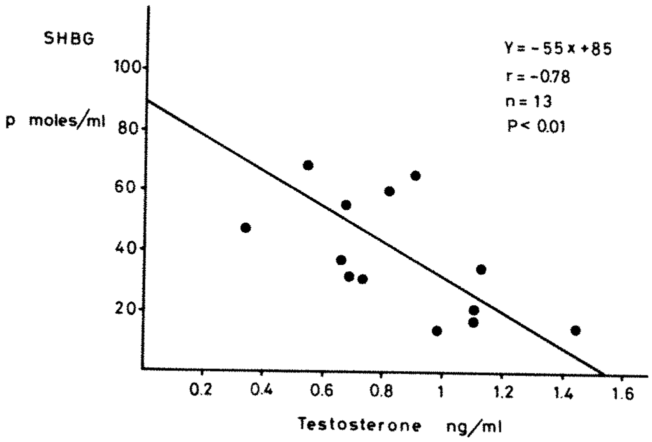


FIG. 1a. Relationship between plasma testosterone concentration and SHBG binding in premenopausal breast cancer patients.

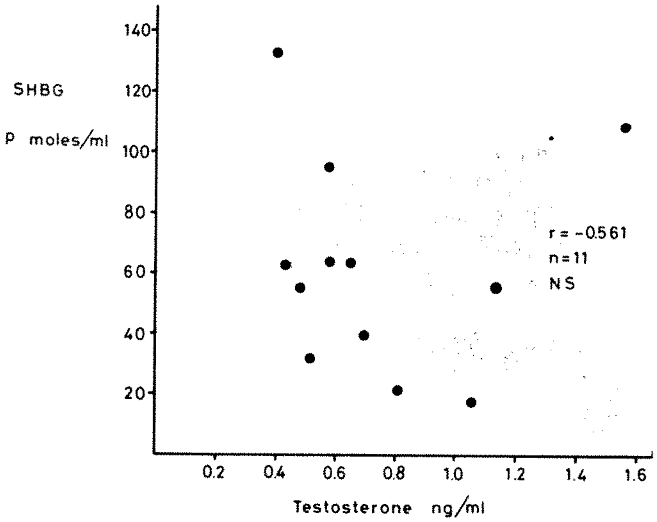


FIG. 1b. Relationship between plasma testosterone concentration and SHBG binding in postmenopausal breast cancer patients.

Relationship Between SHBG and CER (Group B)

In premenopausal CER-positive and negative patients, the SHBG plasma concentrations were 59 ± 12 (mean ± SD) p moles/ml of plasma and 28 ± 7 (mean ± SD) p moles/ml of plasma, respectively. The concentration difference was significant ($p < 0.05$) (Fig. 2).

The plasma SHBG concentration in the premenopausal controls was 52 ± 11 (mean ± SD) p moles/ml of plasma and concentration difference between the controls and premenopausal CER-negative patients was significant ($p < 0.05$). There was no significant difference between the controls and premenopausal CER-positive patients.

Plasma SHBG concentration in the postmenopausal controls, CER-positive and negative patients was 35 ± 76 (mean ± SD) p moles/ml of plasma, 71 ± 34 (mean ± SD) p moles/ml of plasma, and 34 ± 8 (mean ± SD), respectively.

There was a significant difference between postmenopausal CER-positive and negative ($p < 0.05$) and between postmenopausal CER-positive patients and postmenopausal controls ($p < 0.01$). Between postmenopausal CER-negative patients and controls, there was no significant difference in plasma SHBG concentration (Fig. 2).

Plasma SHBG Concentration Prior to Hormone Therapy (Group C)

Ninety-one per cent of the tumors which showed high SHBG concentration (premenopausal: >60 p moles/ml of plasma, postmenopausal: >50 p moles/ml of plasma) responded well, while only 18% of the tumors with low SHBG concentration (premenopausal: <60 p moles/ml of plasma, postmenopausal: <50 p

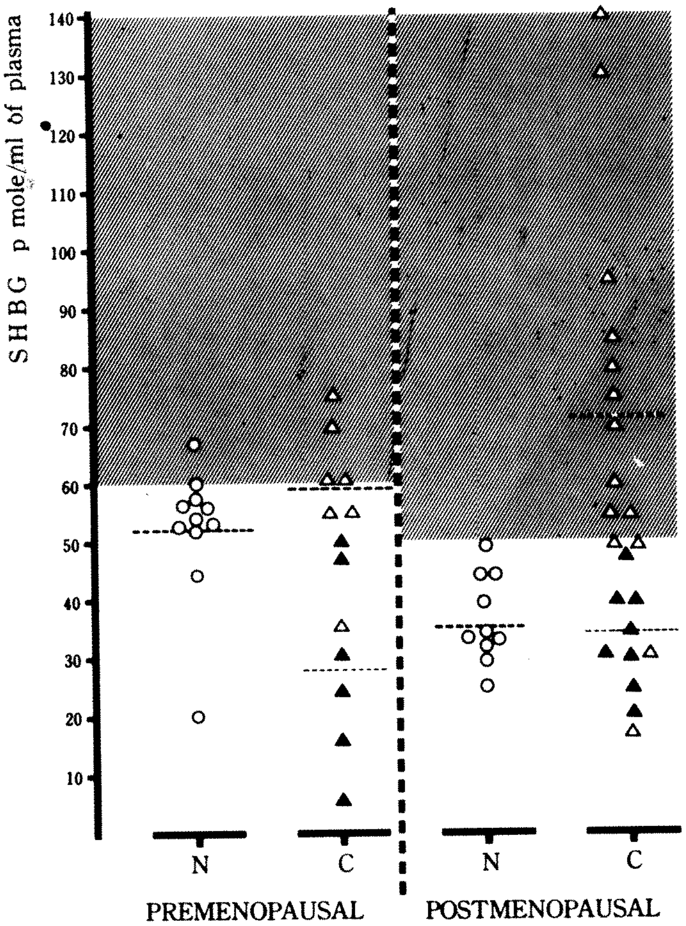


FIG. 2. Relationship between plasma SHBG binding capacity and cytosol estrogen receptors. ○: Normal females (premenopausal N = 11, postmenopausal N = 10). △: Estrogen receptor positive patients (premenopausal N = 7, postmenopausal N = 14). ▲: Estrogen receptor negative patients (premenopausal N = 6, postmenopausal N = 8). Premenopausal: last menstruation <1 year. Postmenopausal: last menstruation >1 year. N: Normal controls. C: Breast cancer. Shaded area: High SHBG area. Broken line: Mean value.

moles/ml of plasma) responded well to the various types of hormone therapy (Table 1).

In premenopausal patients, 88% of the tumors with high and 13% of those with low SHBG concentration responded well to hormone therapy. In postmenopausal patients, 92% of the tumors with high and 18% of those with low SHBG concentration responded well to hormone therapy.

The SHBG titer was determined before hormone therapy or mastectomy to discover whether a correlation exists between SHBG titer and hormone dependence of the tumors. In ovariotomy patients and those receiving androgen therapy, SHBG titer was 100% reliable in predicting tumor response to hormone therapy, in adrenalectomy patients, predictability was 77% and in patients receiving estrogen therapy, predictability was 84%.

We noted a statistical difference between the mean value of SHBG binding capacity in hormone responsive and nonresponsive tumors ($p < 0.01$) (Table 2).

Twenty-five per cent of the hormone responsive tumors showed complete remission, however, there was no statistical difference between the mean value of SHBG binding capacity of tumors which showed complete and that of tumors which showed only partial remission.

Discussion

Bodard, et al.[3] suggested that SHBG may be a glycoprotein larger in molecular size than albumin or transferrin and that the binding specificity of SHBG is different from other sex steroid binding proteins found in tissue. Changes in endogenous steroid levels affect the binding capacity of SHBG, therefore, the binding capacity of plasma SHBG is a reliable indicator of the endogenous sex steroid levels.

Relationship Between Testosterone Plasma Concentration and SHBG Binding Capacity (Group A)

Burke and Anderson[5] and Covol, et al.[6] reported that endogenous sex steroid levels affect SHBG binding capacity. Others suggested that in normal subjects, there is a positive correlation between estrogen plasma concentration and SHBG binding capacity and a negative correlation between plasma testosterone concentration and SHBG binding capacity.[1,5,6,12,20,27] In some disorders such as hyperthyroidism,[23] hirsutism,[5] polycystic ovarian syndrome,[21] liver disease,[22,23] and breast cancer treated with estrogen or androgen therapy, abnormal SHBG binding capacity was observed.

However, to date no studies have been reported on the relationship between SHBG binding capacity and plasma testosterone concentration in breast cancer.

TABLE 1. *SHBG Binding Capacity in Advanced Breast Cancer and Tumor Regression After Hormone Therapy*

SHBG Binding Capacity Prior to Therapy	Therapy (N = 50)				Posttherapy Regression
	Ovariotomy (N = 7)	Adrenalectomy (N = 13)	Estrogen (N = 25)	Androgen (N = 5)	
High	3/3	4/5	10/11	3/3	20/22 (91%)
Low	0/4	2/8	3/14	0/2	5/28 (18%)

The present study indicates that there is a significant negative correlation between SHBG binding capacity and plasma testosterone concentration in breast cancer patients as well as in normal individuals.[12]

Relationship Between SHBG and CER (Group B)

We found that all breast cancer patients with high SHBG titers were CER-positive (Fig. 2). This finding supports our hypothesis that an increase in SHBG initiates and promotes estrogen receptor synthesis in human breast cancer. Bayard et al.[2] previously noted that a change in estrogen receptor levels is associated with human endogenous estrogen and progesterone levels.

Our data are consistent with those obtained in experimental studies.[4,8,9,15,16] The high estradiol and progesterone receptor levels during the late proliferative phase coincide with a rapid increase in plasma estradiol levels, suggesting that a high concentration of plasma estradiol induces the synthesis of estrogen receptors.

Plasma SHBG Concentration Prior to Hormone Therapy (Group C)

Our results indicate that pretherapy SHBG titers are reliable indicators in determining the efficacy of hormone therapy.[18]

In this method, 60 μl of plasma are sufficient for obtaining SHBG titers and the hormone sensitivity of breast tumors can be detected even if tumor tissue is not available for receptor analysis. Furthermore, the method of plasma SHBG determination is effective in premastectomy primary breast cancer patients as an indicator of primary tumor hormone dependence, as well as in recurrent tumors. The method of determining SHBG titer prior to initiation of therapy is counter-indicated, however, in patients with endocrine diseases which may have effected a change in SHBG levels.[20-23]

Ninety-one per cent of the patients who had high SHBG titers responded well to hormone therapy. Thirty-three per cent of the patients with low SHBG titers were CER-positive, however, only 18% of all patients with low SHBG titers responded to hormone therapy, indicating that the presence of CER alone does not guarantee that the tumor is hormone dependent. These findings support our second hypothesis that the presence of estrogen receptors and an endogenous hormone environment which reacts to the receptor system are necessary for the tumor to be hormone dependent.

TABLE 2. *SHBG Binding Capacity in Advanced Breast Cancer and Response to Hormone Therapy*

	SHBG Binding Capacity (mean ± SD): p mole/ml		
	Responsive	Non-responsive	
Premenopausal	64 ± 11 N = 9	40 ± 14 N = 8	$p < 0.01$
Postmenopausal	54 ± 11 N = 16	33 ± 10 N = 17	$p < 0.01$

SD: Standard Deviation.

Binding capacity is in p mole/ml of plasma. The statistical difference was tested utilizing Student's paired t-test.

Acknowledgments

The authors wish to thank Dr. H. Kaneko and Dr. K. Hayashi for their support and valuable suggestions. We are also indebted to Professor K. Asano and Ms. U. Petralia for reviewing the manuscript.

References

1. Akande, E. O. and Anderson, D. C.: Role of Sex Hormone Binding Globulin in Hormonal Changes and Amenorrhoea in Thyrotoxic Women. Br. J. Obstet. Gynecol., 82:557, 1975.
2. Bayard, F., Damilano, S., Robel, P. and Baulieu, E. E.: Cytoplasmic and Nuclear Estradiol and Progesterone Receptors in Human Endometrium. J. Clin. Endocrinol. Metab., 46: 635, 1978.
3. Bodard, C. M., Alfsen, A. and Baulieu, E. E.: Sex Steroid Binding Plasma Protein. Karolinska Symposia on Research Methods in Reproductive Endocrinology, 2nd Symposium, Steroid Assay by Protein Binding, March 23–25, 1970.
4. Brenner, R. M., Resko, J. A. and West, N. B.: Cyclic Changes in Oviductal Morphology and Residual Cytoplasmic Estradiol Binding Capacity Induced by Sequential Estradiol Progesterone Treatment of Spayed Rhesus Monkeys. Endocrinology, 95:1094, 1974.
5. Burke, C. W. and Anderson, D. C.: Sex Hormone Binding Globulin is an Estrogen Amplifier. Nature, 240:38, 1972.
6. Corvol, P. L., Chrambach, A., Rodbard, D. and Bardin, C. W.: Physical Properties and Binding Capacity of Testosterone Estradiol Binding Globulin in Human Plasma, Determined by Polyacrylamide Gel Electrophoresis. J. Biol. Chem., 246:3435, 1971.
7. Erlanger, B. F., Borek, F., Beiser, S. M. and Lieberman, S.: Steroid-protein Conjugates. I. Preparation and Characterization of Conjugates of Bovine Serum Albumin with Testosterone and with Cortisone. J. Biol. Chem., 228:713, 1957.
8. Feil, P. D., Glasser, S. R., Toft, D. O. and O'Malley, B. W.: Progesterone Binding in the Mouse and Rat Uterus. Endocrinology, 91:738, 1972.
9. Feil, P. D. and Bardin, C. W.: Cytoplasmic and Nuclear Progesterone Receptors in the Guinea Pig Uterus. Endocrinology, 97:1398, 1975.
10. Furuyama, S., Mayes, D. M. and Nugent, C. A.: A radioimmunoassay for Plasma Testosterone. Steroids, 16:415, 1970.
11. Hayward, J. L., Carbone, P. P., Heuson, J. C., et al.: Assessment of Response to Therapy in Advanced Breast Cancer. Japan Mammary Cancer Society, 1977.
12. Horst, H. J., Bartsch, W. and Dirksen-Thedens, I.: Plasma Testosterone, Sex Hormone Binding Globulin Binding Capacity and Per Cent Binding of Testosterone and 5α-dihydrotestosterone in Prepubertal, Pubertal and Adult Males. J. Clin. Endocrinol. Metab., 45:522, 1977.
13. Makino, T.: Radioimmunoassay of Sex Steroid Hormone. Folia Endocrinol. Jap., 49:629, 1973.
14. McGuire, W. L., Carbone, P. P. and Vollmer, E. P.: Estrogen

Receptors in Human Breast Cancer. North-Holland Publishing Co., Amsterdam, 1975.
15. Mester, J., Martel, D., Psychoyos, A. and Baulieu, E. E.: Hormonal Control of Estrogen Receptor in Uterus and Receptivity for Ovo-implantation in the Rat. Nature, 250: 776, 1974.
16. Milgrom, E., Atger, E., Perrot, M. and Baulieu, E. E.: Progesterone in Uterus and Plasma. VI. Uterine Progesterone Receptors During the Estrus Cycle and Implantation in the Guinea Pig. Endocrinology, 90:1071, 1972.
17. Milgrom, E., Luu Thi, M., Atger, M. and Baulieu, E. E.: Mechanisms Regulating the Concentration and the Conformation of Progesterone Receptor(s) in the Uterus. J. Biol. Chem., 248:6366, 1973.
18. Murayama, Y., Utsunomiya, J. and Asano, K.: Sex-hormone Binding Globulin Predicts Response of Breast Cancer to Hormone Therapy. Lancet, 2:1356, 1977.
19. Murayama, Y., Sakuma, T., Udagawa, H., et al.: Sex Hormone Binding Globulin and Estrogen Receptor in Breast Cancer. J. Clin. Endocrinol. Metab., 46:998, 1978.
20. Rosenfield, R. L.: Plasma Testosterone Binding Globulin and Indexes of the Concentration of Unbound Plasma Androgens in Normal and Hirsute Subjects. J. Clin. Endocrin. Metab., 32:717, 1971.
21. Southern, A. L., Gordon, G. G., Tochimoto, S., et al.: Testosterone and Androstenedione Metabolism in the Polycystic Ovary Syndrome: Studies of the Percentage Binding of Testosterone in Plasma. J. Clin. Endocrinol. Metab., 29: 1356, 1969.
22. Thiel, D. H. V., Gavaler, J. S., Lester, R., et al.: Plasma Estrone, Prolactin, Neurophysin, and Sex Steroid Binding Globulin in Chronic Alcoholic Men. Metabolism, 24:1015, 1975.
23. Tulchinsky, D. and Chopra, I. J.: Competitive Ligand Binding Assay for Measurement of Sex Hormone Globulin (SHBG). J. Clin. Endocrinol. Metab., 37:873, 1973.
24. Wagner, R. K.: Characterization and Assay of Steroid Hormone Receptor and Steroid Binding Serum Proteins by Agar Gel Electrophoresis at Low Temperature. Physiol. Chem., 353: 1235, 1972.
25. Wagner, R. K. and Jungblut, P. W.: Oestradiol and Dihydrotestosterone Receptors in Normal and Neoplastic Human Mammary Tissue. Acta Endocrinol., 82:105, 1976.
26. Wu, C. H. and Lundy, L. E.: Radioimmunoassay of Plasma Estrogens. Steroids, 18:91, 1971.
27. Wu, C. H., Motohashi, T., Abdel-Rahman, H. A., et al.: Free and Protein-bound Plasma Estradiol 17β During the Menstrual Cycle. J. Clin. Endocrinol. Metab., 43:436, 1976.

Essential Fatty Acid Deficiency in Total Parenteral Nutrition

Detection by Changes in Intraocular Pressure

HERBERT FREUND, M.D.,* NAVA FLOMAN, M.D., BERNARD SCHWARTZ, M.D., PH.D., JOSEF E. FISCHER, M.D.

Essential fatty acid deficiency (EFAD) has been commonly and readily diagnosed during fat-free total parenteral nutrition (TPN), with only vague awareness of possible functional and clinical derangements secondary to essential fatty acid deficiency. Arachidonic acid is known to be a precursor for prostaglandin (PG) synthesis. Prostaglandins are known to be intermediaries between stimulus and cellular response in a variety of physiologic and pathologic processes; one would suspect therefore that EFAD would result in PG deficiency with resultant multiple derangements in functions regulated by PG. We tested this hypothesis by serially measuring intraocular pressure (IOP) in patients before and during fat-free TPN and after supplementing these patients with fat. In the eye as well as in various other organs PG are believed to act as mediators of adrenergic neurotransmission by a negative feedback mechanism. As catecholamines are potent ocular hypotensive agents, decreased levels of PG due to EFAD will cause increase in catecholamine turnover with a reduction in IOP. Two groups of patients matched as to their age, sex, nutritional status and diseases were studied. One group (control) was receiving a normal diet or fat-containing TPN while the other group was receiving fat-free TPN. IOP in the fat-free TPN group dropped from 13.7 ± 0.4 mmHg pre-TPN to 9.3 ± 0.5 mmHg during the first week of fat-free TPN. Within two weeks after supplementation of fat or return to normal oral diet IOP returned to 13.9 ± 0.3 mmHg. Prostaglandin levels, which were 0.025 ± 0.004 ng/ml pre-TPN or in control patients decreased to 0.012 ± 0.002 ng/ml ($p < 0.001$) during fat-free TPN, to return to normal after fat was added to TPN regime or patients returned to normal oral diet. During fat-free TPN linoleic acid levels decreased to 40% of its initial value with a mild increase upon the addition of fat, while eicosatrienoic acid and the triene:tetraene ratio increased to 6.5 times their initial values. Arachidonic acid levels did not change during fat-free TPN or after repletion with fat. Intraocular pressure determination seem to be a simple, harmless, inexpensive, reliable and sensitive indicator of EFAD. Moreover, IOP determination represent a functional derangement which in a clinical setting lends functional credence to the biochemical changes of EFAD whose entire significance has not yet been determined. Similarly, serial IOP determinations are sensitive in detecting adequate functional repletion of EFAD. As PG are known to act as intermediaries in a variety of physiological processes it seems reasonable to assume that the change in IOP is only one of many different changes and derangements to occur as a result of PG and EFA deficiency.

From the Department of Surgery, Massachusetts General Hospital and Harvard Medical School and the Department of Ophthalmology, New England Medical Center Hospital and Tufts University School of Medicine, Boston, Massachusetts

IN RECENT YEARS essential fatty acid deficiency (EFAD) has been reported in patients treated with fat-free parenteral nutrition.[4,5,11,12,14,16] The symptomatology of EFAD falls into three categories: 1) Clinical manifestations of growth retardation, dermatitis, hair loss and susceptibility to bacterial infections. 2) Histologic changes in kidneys, skin, ovaries and testes. 3) Biochemical abnormalities involving increased levels of 5,8,11-eicosatrienoic acid and decreased levels of linoleic and arachidonic acid.[2,6,8,12,16,17] The biochemical abnormalities are usually the earliest signs of EFAD.[8] Under normal circumstances the body converts linoleic acid (C 18:2 $\omega6$) to arachidonic acid (C 20:4 $\omega6$). In case of linoleic acid deficiency the same enzyme system elongates and desaturates oleic acid (C 18:1 $\omega9$) to produce 5,8,11-eicosatrienoic acid (C 20:3 $\omega9$) rather than arachidonic acid. Arachidonic acid is the precursor of prostaglandin E_2 (PGE_2) and prostaglandin $F_2\alpha$- ($PGF_2\alpha$) which are synthetized in a variety of tissues and participate in multiple physiologic processes as intermediaries between stimulus and cellular response. Because of their widespread distribution and multiplicity of effects they have been implicated in a great variety of physiologic and pathologic processes, among them the regulation of intraocular pressure (IOP). It is therefore to be expected that EFAD states will result in a decrease in prostaglandin synthesis. Indirect evi-

---

* Present address: Department of Surgery, Hebrew University—Madassah Medical Center, Jerusalem, Israel.

Reprint requests to: Josef E. Fischer, M.D., Professor & Chairman, Department of Surgery, University of Cincinnati Medical Center, 231 Bethesda Avenue, Cincinnati, Ohio 45267.

Submitted for publication: December 6, 1978.

0003-4932/79/0800/0139 $00.75 © J. B. Lippincott Company

TABLE 1. *Diagnosis of Patients Studied*

	Fat-free TPN Group	Control Group
Cancer, lymphoma	8	7
Inflammatory bowel disease	8	5
Gastrointestinal fistulas	2	1
Abdominal aortic aneurism	2	—
Diverticulitis	1	2
Cirrhosis of liver	—	2
Infection, sepsis, abscess	2	2
Sprue	—	1
Anorexia nervosa	1	—
Multiple trauma	1	—

dence for this assumption has been offered in EFA deficient rats reported to have a reduced inflammatory response, a function known to be prostaglandin mediated.[1,3]

The prostaglandins are believed to act as important mediators in the adrenergic transmission system by a negative feedback mechanism.[7] It has been shown in rats that inhibition of prostaglandin synthesis results in increased norepinephrine turnover. Likewise, animals exhibiting low prostaglandin levels as a result of EFAD can be expected to have an increased catecholamine turnover. The catecholamines are important regulators of ocular neuromuscular transmission,[10] and potent ocular hypotensive agents, (widely used in the treatment of glaucoma) believed to exert their hypotensive effect by decreasing aqueous flow into the anterior chamber of the eye.[20] An increase in catecholamine turnover in the eye, expected to occur in EFA and PG deficient patients, should eventually result in reduction of IOP.

We examined the changes in IOP, fatty acid levels and plasma prostaglandin E_2 metabolite levels before and during fat-free total parenteral nutrition (TPN). Chemical EFAD occurred early in the course of fat-free TPN, resulting in a significant decrease in IOP and PGE_2 levels. The administration of fat in EFA deficient patients restored IOP and PGE_2 levels to normal.

These results suggest that serial determinations of intraocular pressure may be a simple, noninvasive means of detecting and following essential fatty acid deficiency during parenteral nutrition.

Materials and Methods

Two groups of patients were studied: *Group I—Fat-free TPN group* included 25 patients hospitalized at the Massachusetts General Hospital who received total parenteral nutrition without fat for various periods of time (Table 1). Parenteral nutrition in this group included a mixture of crystalline amino acids, hypertonic glucose, electrolytes and vitamins but no fat. These patients had their intraocular pressure measured repeatedly during the course of parenteral nutrition. Some of the patients had their IOP measured also before starting TPN and/or during supplementation of TPN with a fat solution (Intralipid 10%) or when put back on normal oral fat containing diet. *Group II—Control group* included 20 patients matched as to their sex, age (Table 2), nutritional status and diagnosis (Table 1) to Group I patients. However, the patients in this group were receiving either normal oral diet or TPN supplemented with fat during the course of their disease. Parenteral nutrition in this group consisted of a mixture of crystalline amino acids, hypertonic glucose, electrolytes, vitamins and 500 ml of Intralipid 10% 2–3 times/week.

Intraocular Pressure Determination

Intraocular pressure was measured as a bedside procedure by the Schoitz tonometer® with both 5.5 mg and 10.0 mg weights using ophthalmic Proparacaine hydrochloride 0.5% for local anesthesia. Determinations were always performed by the same ophthalmologist at the same time of the day (10–12 AM).

Prostaglandin Determinations

Prostaglandin levels were determined by a radioimmunoassay measuring a PGE_2 metabolite (13,14-dihydro-15-keto prostaglandin E_2), using a specific antiserum.[9] 13,14-dihydro-15-keto PGE_2 levels were determined in the plasma of eight pre-TPN and control patients, in seven patients during fat-free TPN and in ten patients who were returned to normal oral diet or in whom fat was added to their TPN regime.

Fatty Acid Determinations

Blood for fatty acid determination was drawn into heparinized tubes, centrifuged and the plasma frozen until analysis, performed by extraction and gas liquid chromatography of total plasma lipids. Fatty acids were determined in seven control patients, in four patients during fat-free TPN and in six patients in whom fat was added to their TPN regime or who were put back on normal diet after a period of fat-free TPN. All results are given as mean ± SEM and statistical significance was determined by Student's t-test. These studies were approved by the Human Studies Committee of the Massachusetts General Hospital and informed consent was obtained.

TABLE 2. *Distribution of Patients*

	Fat-free TPN Group	Control Group
Number of patients	25	20
males	11	10
females	14	10
Average age of patients	55.5 years	54.0 years
Age range	22–75 years	28–80 years

Results

Intraocular Pressure Changes (IOP)

Mean IOP was 13.7 ± 0.4 mmHg in the fat-free TPN group and 14.4 ± 0.3 mmHg in the control group before the initiation of TPN (normal IOP 14 ± 0.5). In the fat-free TPN group IOP pressure dropped within the first week to 9.3 ± 0.5 mmHg ($p < 0.001$). Similarly low pressures ranging from 8.2–10.2 mmHg were maintained during fat-free TPN periods of up to 16 weeks (Fig. 1). After the initial drop in IOP occurring within the first week of fat-free TPN, no further significant drop in IOP occurred and the pressures during the following weeks are very similar (Fig. 1). IOP in the fat-free TPN group returned to pre-TPN levels (13.9 ± 0.3 mmHg) when patients were returned to normal oral diet or fat was added to their TPN regime, the pressures being significantly higher than during fat-free TPN ($p < 0.001$). IOP returned to normal after supplementation of fat within 2.2 ± 0.2 weeks. However as IOP determinations were performed only every seven to ten days this figure is misleading as IOP may have returned to normal after a shorter period of fat supplementation.

Prostaglandin Determination

With the decrease in IOP a simultaneous decrease in prostaglandin (PGE_2) metabolite level was noted (Fig. 2). PGE_2 metabolite levels dropped from 0.025 ± 0.004 ng/ml in the pre-TPN and control patients to 0.012 ± 0.002 ng/ml during fat-free TPN ($p < 0.001$). A normal oral diet or the addition of fat to the TPN regime resulted in an increase in plasma PGE_2 metabolites levels to 0.024 ± 0.002 ng/ml, similar to the pre-TPN or control levels (Fig. 2).

Fatty acid determination

Figure 3 illustrates the alterations in linoleic acid (18:2 ω6), arachidonic acid (20:4 ω6), eicosatrienoic acid (20:3 ω9) and the triene:tetraene ratio occurring during the course of fat-free TPN and after the addition of intravenous fat or normal diet to patients who were on fat-free TPN. As is evident from Figure 3 not all the fatty acids examined behaved alike. Whereas linoleic acid levels dropped during fat-free TPN to about 40% of its levels prior to TPN or its levels in patients on fat-containing TPN, arachidonic acid levels did not change. However, the drop in linoleic acid levels, was not statistically significant due to the wide variation of the numbers (range 56.5–188.0 μg/ml), pointing to the difficulty of evaluating essential fatty acid deficiency. Similar variability was shown by 5,8,11-eicosatrienoic acid levels which ranged from 0–20.0 μg/ml in control patients. However the levels of 5,8,11-eicosatrienoic acid in fat-free TPN increased significantly compared to pre-TPN of fat containing TPN patients ($p < 0.001$). Furthermore, many patients showed a mixed pattern, *i.e.* high levels of arachidonic acid, linoleic acid as well as eicosatrienoic acid during repletion with fat while others showed low levels of arachidonic, linoleic and eicosatrienoic acids in the control group or fat-repleted TPN group. The triene:tetraene ratio was 0.11 ± 0.05 in the control patients, rose to 0.78 ± 0.18 in EFAD patients ($p < 0.001$) and decreased

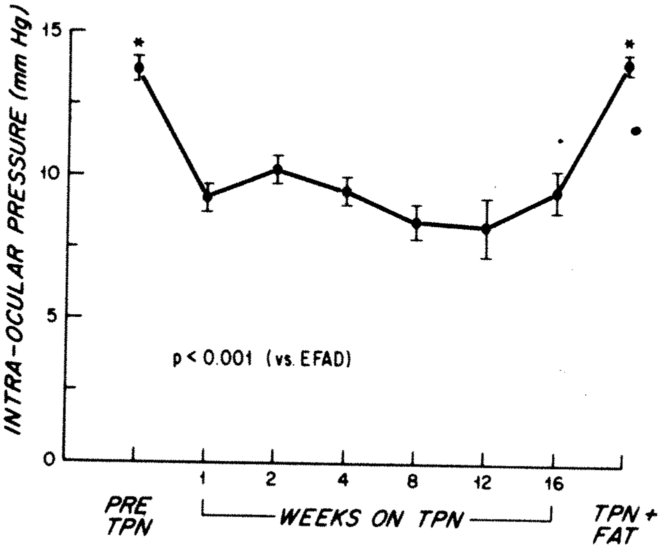


FIG. 1. Intraocular pressure (mmHg) before and during fat-free total parenteral nutrition and after adding Intralipid 10% to the TPN regime. Pressures before TPN and after repletion with fat are both significantly higher than during essential fatty acid deficiency ($p < 0.001$).

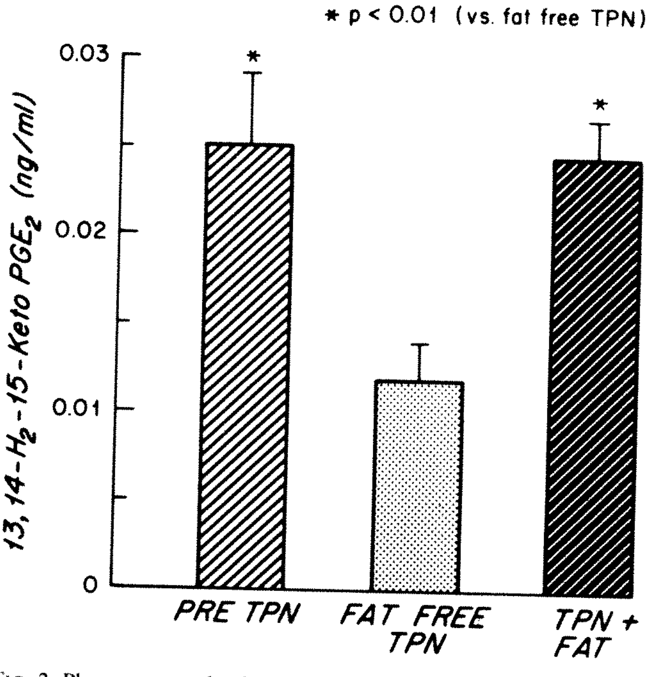


FIG. 2. Plasma prostaglandin E_2 metabolite levels before and during fat-free total parenteral nutrition and after adding Intralipid 10% to the TPN regime. Levels during fat-free TPN are significantly ($p < 0.01$) lower than in control patients or after repletion with fat.

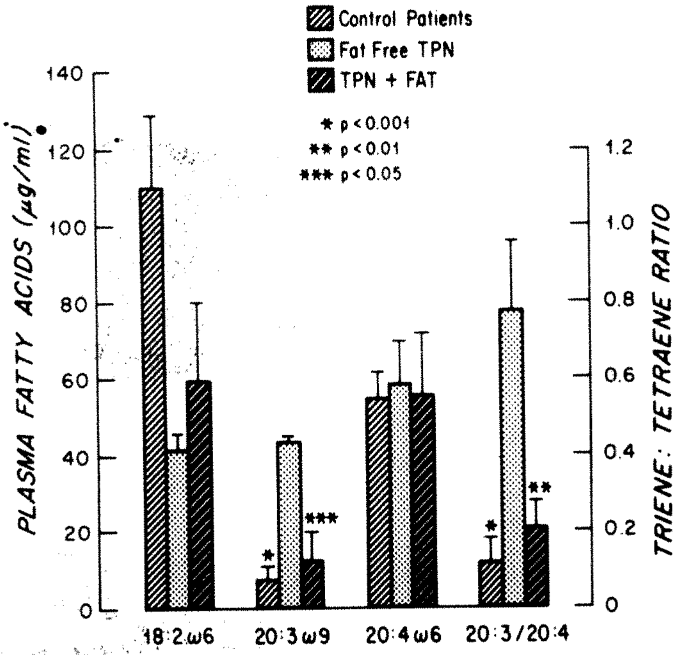


FIG. 3. Plasma levels of linoleic acid (18:2 ω6), arachidonic acid (20:4 ω6), 5,8,11 eicosatrienoic acid (20:3 ω9) and the triene:tetraene ratio in patients before and during fat-free total parenteral nutrition and after supplementation with Intralipid 10%. There is a drop in linoleic acid with a rise in eicosatrienoic acid and the triene:tetraene ratio during fat-free TPN with partial reversal of these changes upon repletion with Intralipid 10%.

to 0.21 ± 0.07 after the addition of fat or normal diet ($p < 0.01$) (Fig. 3).

Discussion

Essential fatty acid deficiency (EFAD) is a complication of fat-free parenteral nutrition occurring both in infants and adults.[2,4,11-14] The diagnosis of EFAD is based on clinical features such as the appearance of scaly skin rash, sparse hair growth or failure to thrive, which occur late in the course of EFAD, and biochemical features occurring within two weeks of fat-free diet.[5,16] The only essential fatty acid in man is linoleic acid (18:2 ω6) which may be elongated and desaturated to form arachidonic acid (20:4 ω6). Arachidonic acid is known to be the precursor of prostaglandin E_2 (PGE_2) and $F_2\alpha$($PGF_2\alpha$) formed as a result of prostaglandin synthetase activity. The prostaglandins appear to act as intermediaries between stimulus and cellular response. Because of their widespread distribution and multiplicity of effects they have been implicated in a variety of physiological and pathological processes. This close relationship between essential fatty acids and prostaglandins could theoretically result in patients with EFAD in widespread functional derangements resulting from prostaglandin deficiency. In addition, 5,8,11-eicosatrienoic acid (20:3 ω9), known to increase significantly during EFAD, was found to be a strong inhibitor of prostaglandin synthesis.[19] Indirect evidence to that effect was presented in EFA deficient rats exhibiting a reduced inflammatory reaction, known to be prostaglandin mediated.[1,3] The injection of very low concentrations of various prostaglandins resulted in enhancement of this poorly developed inflammatory response to the same extent as seen in normal rats.[15] In the eye, as well as in various other organs, prostaglandins are believed to act as mediators of adrenergic neurotransmission by a negative feedback mechanism.[7,10] As catecholamines are potent ocular hypotensive agents, believed to exert their hypotensive effect by decreasing aqueous inflow into the anterior chamber of the eye,[20] decreased levels of prostaglandins, due to lack of substrate or inhibition of synthesis in EFA deficient patients, causing an increase in catecholamine turnover, will eventually result in a reduction of intraocular pressure (IOP). We were able to test this hypothesis by serially measuring IOP in patients before, during and after fat-free TPN, comparing them to patients with the same disease states and nutritional status who were either supplemented with fat during TPN or were able to take normal oral diet. Determination of IOP is a simple and reliable bed-side procedure which can be repeated as often as necessary without causing any harm or discomfort to the patient. In this study we found a good correlation between IOP, plasma prostaglandin levels, and plasma concentrations of some of the fatty acids. Within one week of the initiation of fat-free TPN, IOP decreased significantly and remained low for as long as 16 weeks, returning to normal levels upon supplementation with intravenous or oral fat. Plasma PGE_2 metabolite levels decreased to 46% of their initial pre-TPN level during fat-free TPN ($p < 0.01$) and returned to normal levels within two weeks after the addition of intravenous fat to the TPN regime or the return to normal diet. The fatty acids correlated only partially with the IOP and prostaglandin levels. The changes in fatty acids are similar to those described by Wene, et al.[16] who also did not find any consistent change in arachidonic acid (20:4 ω6) between normal, EFA deficient and fat-repleted patients. Linoleic acid (18:2 ω6) levels varied considerably resulting in a nonsignificant, although quite distinct decrease in its plasma levels in EFA deficient patients, with only a mild increase upon the addition of fat. The 5,8,11 eicosatrienoic acid plasma concentrations were significantly increased in EFA deficient patients resulting also in an increased triene: tetraene ratio ($p < 0.001$). With the addition of fat, eicosatrienoic acid levels and the triene:tetraene ratio decreased although they did not return entirely to normal.

This rise in 5,8,11-eicosatrienoic acid levels is important not only as an early biochemical indicator of EFAD but primarily as a strong inhibitor of prostaglandin synthesis.[19] In this respect it might well be that we are dealing not only with lack of substrate for arachidonic acid and prostaglandin synthesis but also and probably mainly with a block in prostaglandin synthesis by eicosatrienoic acid (20:3 ω9). This block in prostaglandin synthesis can also explain in part the near-normal levels of arachidonic acid. As less prostaglandins are synthesized due to the inhibition by eicosatrienoic acid, there is an accumulation of unused arachidonic acid pushing back towards normal the level of this actually deficient fatty acid.

We are thus in agreement with Wene, et al.[16] and Goodgame, et al.[5] that the definition of EFAD is somewhat arbitrary and indistinct. Considering that fatty-acid determinations are expensive, somewhat complicated and perhaps not entirely informative in evaluating patients' state of deficiency, we would like to suggest the determination of intraocular pressure as a useful alternative. It is sensitive, reproducible, inexpensive, and in our opinion offers a reasonable indication of EFA deficiency. In the patients reported, intraocular pressure decreased sharply within one week of initiation of TPN, while Goodgame, et al.,[5] Wene, et al.[16] and others were able to detect EFAD only after two weeks. In this respect IOP determinations may be a more sensitive indicator of EFAD. Moreover, it represents an early functional counterpart to biochemical changes. Serial IOP determination appears useful in detecting adequate functional repletion of EFA deficiency as well. In this study IOP returned to normal within two weeks after fat supplementation. However, as IOP was measured at seven to ten day intervals the return to normal might have occurred even earlier.

The decrease in PGE_2 levels in EFA deficient patients during TPN with the resultant decrease in IOP points to the possibility of many more and diverse functional derangements occurring in EFA deficient patients. As prostaglandins are known to act as intermediaries between stimulus and cellular response in a variety of processes, it seems reasonable to assume that the change in IOP is only one of many different changes and derangements to occur as a result of prostaglandin and EFA deficiency. In this respect it is interesting to note that Ziboh and Hsia[18] reported clearing of scaly lesions in the skin of EFA deficient rats with topical application of PGE_2.

Most recent studies confirm that EFAD is chemically detectable after one to two weeks of lipid-free parenteral nutrition.[5,11,13,16] Animal and clinical data suggest that anywhere between 2–20% of the total supplied calories should be given as fat.[8,11,13,14] However, most authors agree that 2–5% is sufficient.

The existence of a functional counterpart to what has heretofore been principally a biochemical lesion argues for the early use of essential fatty acids in total parenteral nutrition either intravenously or orally. Derangements in prostaglandins leading to alterations in ocular dynamics is likely but one of many potentially damaging complications of EFAD which should be avoided.

Acknowledgment

We thank Dr. L. Levine of Brandeis University for his advice and assistance.

References

1. Bonta, J. L., Paunhan, M. J. and Adolfs, M. J. P.: Reduced Exudation and Increased Tissue Proliferation During Chronic Inflammation in Rats Deprived of Endogenous Prostaglandin Precursors. Prostaglandins, 14:295, 1977.
2. Caldwell, M. D., Johnson, H. T. and Othersen, H. B.: Essential Fatty Acid Deficiency in an Infant Receiving Prolonged Parenteral Alimentation. Pediatrics, 81:894, 1972.
3. Denko, C. W.: Effect of Prostaglandins in Urate Crystal Inflammation. Pharmacology, 12:331, 1974.
4. Fleming, C. R., Smith, L. M. and Hodges, R. E.: Essential Fatty Acid Deficiency in Adults Receiving Total Parenteral Nutrition. Am. J. Clin. Nutr., 29:976, 1976.
5. Goodgame, J. T., Lowry, S. F. and Brennan, M. F.: Essential Fatty Acid Deficiency in Total Parenteral Nutrition: Time Course of Development and Suggestions for Therapy. Surgery, 84:271, 1978.
6. Guarnieri, M. and Johnson, R. M.: The Essential Fatty Acids. Adv. Lipid Res., 8:115, 1970.
7. Hedquist, P.: Basic Mechanisms of Prostaglandin Action on Autonomic Neurotransmission. Ann. Rev. Pharmacol. Toxicol., 17:259, 1977.
8. Holman, R. T.: Essential Fatty Acid Deficiency. *In* Progress in the Chemistry of Fat and Other Lipids. Elmsford, Pergamon Press Inc. 1968. p. 279.
9. Levine, L.: Levels of 13,14 Dihydro-15 Keto PGE_2 in Some Biological Fluids as Measured by Radioimmunoassay. Prostaglandins, 14:1125, 1977.
10. Neufeld, A. H. and Page, E. D.: Regulation of Adrenergic Neuro-muscular Transmission in the Rabbit Iris. Exp. Eye Res., 20:549, 1975.
11. O'Neill, J. A., Caldwell, M. D. and Meng, H. C.: Essential Fatty Acid Deficiency in Surgical Patients. Ann. Surg., 185: 535, 1977.
12. Paulsrud, J. R., Pensler, L., Whitten, C. F., et al.: Essential Fatty Acid Deficiency in Infants Induced by Fat-free Intravenous Feeding. Am. J. Clin. Nutr., 25:897, 1972.
13. Postuma, R., Pease, P. W. B., Watts, R., et al.: Essential Fatty Acid Deficiency in Infants Receiving Parenteral Nutrition. J. Ped. Surg., 13:393, 1978.
14. Richardson, T. J. and Sgoutas, D.: Essential Fatty Acid Deficiency in Four Adult Patients During Total Parenteral Nutrition. Am. J. Clin. Nutr., 28:258, 1975.
15. Van Dorp, D. A.: Recent Developments in the Biosynthesis and the Analysis of Prostaglandins. Ann. N.Y. Acad. Sci., 180:181, 1971.
16. Wene, J. D., Connor, W. E. and DenBesten, L.: The development of Essential Fatty Acid Deficiency in Healthy Man Fed Fat-free Diets Intravenously and Orally. J. Clin. Invest., 56:127, 1975.
17. White, H. B., Turner, M. D., Turner, A. C. and Miller, R. C.: Blood Lipid Alterations in Infants Receiving Intravenous Fat-free Alimentation. J. Pediatr., 83:305, 1973.
18. Ziboh, V. A. and Hsia, S. L.: Effects of Prostaglandin E_2 on Rat Skin: Inhibition of Sterol Ester Biosynthesis and Clearing of Scaly Lesions in Essential Fatty Acid Deficiency. J. Lipid Res. 13:458, 1972.
19. Ziboh, V. A., Vanderhoek, J. Y. and Lands, W. E. M.: Inhibition of Sheep Vesticular Gland Oxygenase by Unsaturated Fatty-acids From Skin of Essential Fatty Acid Deficient Rats. Prostaglandins, 5:233, 1974.
20. Zimmerman, T. J. and Chung, C. Y.: Ocular Autonomic Hypotensive Drugs. Curr. Concepts Ophthal., 5:216, 1975.

Effect of Protein Depletion and Repletion on Liver Structures, Nitrogen Content and Serum Proteins

JANET BLANCHARD, M.D., EZRA STEIGER, M.D., MEAGAN O'NEIL, B.A., HERBERT NAITO, PH.D., BRUCE SEBECK, M.D., RAYMOND J. SHAMBERGER, PH.D.

From The Cleveland Clinic Foundation, Cleveland, Ohio

The data presented in this paper demonstrate that a liver which has been severely damaged by protein malnutrition can be restored to normal composition, anatomy and functional capability by central venous feeding. An atypical serum protein electrophoretic pattern characterizes protein malnutrition. TPN repletion restores all of the protein fractions back to normal except for the gamma globulin levels. Liver nitrogen is a very sensitive index of both protein malnutrition and TPN repletion. The liver is dramatically effected by protein malnutrition and its return toward normal can be achieved by TPN support as demonstrated in this paper.

MALNUTRITION IS CHARACTERIZED by loss of body weight and depletion of body protein content and has been well documented in both animals and man.[4,6] Not all organ systems participate equally in the weight loss and decreased protein content.

In enteral feeding, ingested nutrients are absorbed by the intestinal tract and then carried by the portal vein preferentially to the liver before being distributed to the rest of the major organs. In total parenteral nutrition, (TPN) using the central venous route, nutrients are delivered to the cardiopulmonary system first and then distributed according to arterial blood flow to the other organs including the liver. In this experiment, the effects of both protein malnutrition as well as total parenteral malnutrition on body weight and liver morphology, liver ultrastructure, liver weight, liver nitrogen content and liver functional capacity were evaluated.

Materials and Methods

Thirty-four male Sprague-Dawley rats weighing 229–275 g were used for this experiment (Fig. 1). After ten days of acclimatization to the laboratory, ten rats were weighed and killed immediately. These rats are subsequently referred to as Group I-Control Rats. The other 24 rats (Groups II and III) were placed on a protein-free powdered rat diet in which casein was replaced isocalorically with corn starch (Teklad Mills, Sprague-Dawley, Madison, WI. Modified catalogue number 170590). After six weeks, the rats lost approximately 30% of their starting weight and were then either killed immediately as protein depleted controls (Group II-12 rats) or protein repleted intravenously for seven days using a previously described mode for TPN in rats[9] (Group III-12 rats). The TPN fluid used provided 1.76 g of amino acids* and 35.2 carbohydrate kilocalories per day. After the rats were killed they were weighed, their livers weighed and liver segments prepared for light microscopy and electron microscopy and total nitrogen analysis. Serum obtained by cardiac puncture was analyzed for total proteins and serum protein electrophoresis. Liver nitrogen was determined by the Kjeldahl digestion-ammonia method by the Berthelot reaction[1,3] and reported in milligrams per gram of liver.

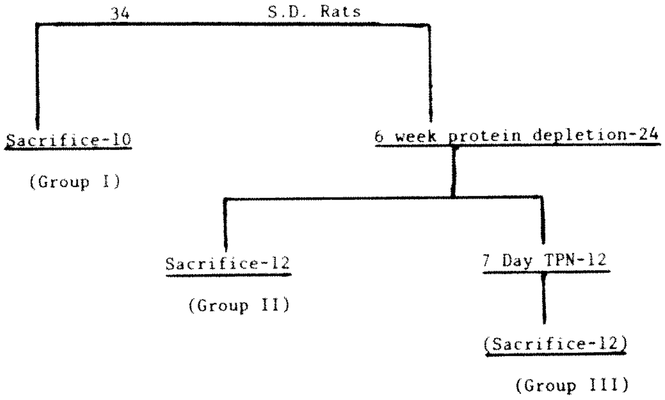


FIG. 1. Effect of protein depletion/repletion on the liver. The following parameters were measured in all groups: 1) body weight, 2) liver weight, 3) liver nitrogen, 4) serum albumin, 5) liver electron micrographs.

---

* Fre-Amine, McGaw Laboratories, California.

Reprint requests: Ezra Steiger, M.D., The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106.
Submitted for publication: January 2, 1979.

0003-4932/79/0800/0144 $00.85 © J. B. Lippincott Company

TABLE 1. *Effect of Protein Depletion on Weight and Serum Proteins*

Group	Diet	Body Weight (g)	Total Protein (g/dl)	Albumin (g/dl)
I	Normal	257 ± 10	5.9 ± .4	3.0 ± .1
		*	*	*
II	Protein-free	174 ± 8	4.7 ± .3	2.1 ± .2
Mean percentage change		32% ↓	20% ↓	30% ↓

* $p < .001$.

TABLE 3. *Effect of Protein Depletion on Serum Globulins*

Group	Diet	Alpha-1	Alpha-2	Beta	Gamma
I	Normal	.66 ± .11	.50 ± .09	1.13 ± .12	.62 ± .13
		**	n.s.	**	*
II	Protein-free	.84 ± .10	.42 ± .13	.81 ± .10	.49 ± .1
Mean percentage change		27% ↑	16% ↓	28% ↓	21% ↓

n.s. = not significant.
* $p < .05$.
** $p < .001$.

Electron micrographs were prepared by taking small specimens (1 mm^3) of liver and immediately fixing in cold 3% glutaraldehyde, rinsing in buffer and post-fixing in osmium tetroxide. Following dehydration in graded alcohol solutions and embedding in epoxy resin, one micron section was stained with Paragon multiple stain and suitable areas were chosen for electron microscopy. Thin sections were stained with uranyl acetate followed by lead citrate and examined in an RCA EMU-4A electron microscope.

Segments of liver from each rat were also fixed in 10% buffered formalin, processed using standard histologic techniques, stained with hematoxylin and eosin and oil red O and examined by light microscopy. Fatty change was graded as absent, mild, moderate or marked with mild representing fatty change in one-third or less of the hepatic parenchymal cells and marked representing fatty change in two-thirds or more of the cells.

Protein Depletion

The affect of protein depletion on weight loss and serum proteins is noted in Table 1. There was a 32% reduction in weight that was reflected by a 30% decrease in serum albumin concentration after six weeks of protein depletion. There was a correspondingly smaller (20%) reduction in total protein. Table 2 shows the significant decrease in liver weight that accompanied the weight loss of protein malnutrition, but even more striking was the 48% reduction in liver nitrogen content. Table 3 shows that protein depletion is accompanied by a significant increase in alpha I globulins and significant decreases in beta and gamma globulins. There was no significant affect on alpha II globulins.

TPN Protein Repletion

Seven days of TPN allowed for significant increases in body weight, total protein, and serum albumin (Table 4). Serum albumin increase paralleled the weight gain. Liver weight (Table 5) did not change with protein repletion but liver nitrogen content markedly increased. The mean percentage increase in liver nitrogen content was twice that of mean body weight increase. Table 6 shows that seven days of TPN protein repletion significantly lowered the elevated alpha I globulin noted in protein deficiency back to normal. Alpha II and beta globulins were significantly increased back to normal levels. However, gamma globulin levels, which were significantly depressed by six weeks of protein depletion (Table 3), were further significantly depressed by TPN protein repletion.

Electron and Light Microscopy

Figure 2a–c represents light micrographs of control liver, protein depleted rats and protein depleted with TPN repletion respectively. There is a striking difference in the amount of fatty change in the protein depleted rats as compared to controls and those with TPN. There is a complete reversal of fatty change with TPN repletion.

TABLE 2. *Effect of Protein Depletion on Liver*

Group	Diet	Body Weight (g)	Liver Weight (g)	Liver Nitrogen (mg)
I	Normal	275 ± 10	8.5 ± .6	125.2 ± 9.8
		**	**	**
II	Protein-free	174 ± 8	6.5 ± .7	65.2 ± 24
Mean percentage change		32% ↓	24% ↓	48% ↓

** $p < .001$.

TABLE 4. *Effect of Protein Repletion on Serum Protein*

Group	Diet	Body Weight (g)	Total Protein (g)	Albumin (g)
II	Protein-free	174 ± 8	4.7 ± .3	2.1 ± .2
		**	*	*
III	TPN	204 ± 16	5.2 ± .5	2.6 ± .5
Mean percentage rate		17% ↑	11% ↑	24% ↑

* $p < .05$.
** $p < .001$.

TABLE 5. *Effect of Protein Repletion on Liver*

Group	Diet	Body Weight (g)	Liver Weight (g)	Liver Nitrogen (mg)
II	Protein-free	174 ± 8	6.5 ± .7	65.2 ± 24
		**	n.s.	*
III	TPN	204 ± 16	6.6 ± 1.1	88.0 ± 9.4
Mean percentage change		17% ↑	1.5% ↑	35% ↑

n.s. = not significant.
* p < .05.
** p < .001.

Figure 3a–c demonstrates electron micrographs of the liver ultrastructure of control rats, protein depleted rats and TPN repleted rats respectively. Figure 3 A demonstrates abundant amounts of parallel strands of rough endoplasmic reticulum (RER) in close association with mitochondria (M) and relatively infrequent strands of smooth endoplastic reticulum (SER). In comparing the ultrastructure of normal control rats with protein depleted rats (Fig. 3b), a marked increase in large intracytoplasmic lipid droplets (L) is noted. In addition to this, there is a marked proliferation of smooth endoplasmic reticulum (SER) and is demonstrated by a meshwork of fine branching tubules. The amount of rough endoplasmic reticulum (RER) is reduced and consists only of a few short profiles adjacent to mitochondria.

After seven days of TPN repletion, there is disappearance of smooth endoplasmic reticulum and again a marked proliferation of the rough endoplasmic reticulum, comparable in amount to the control rats as demonstrated in Figure 3c. Also, a rare lipid droplet persists in these cells.

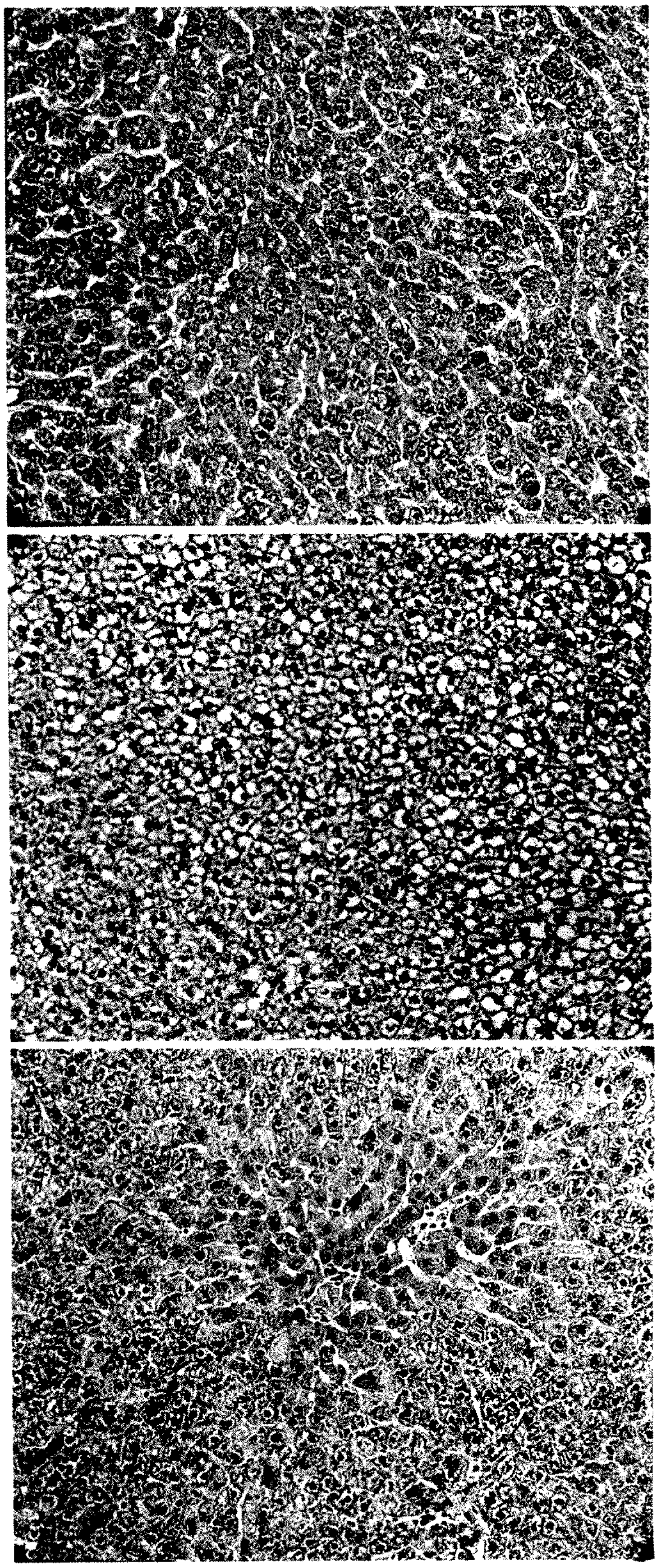
Figures 4a–c again demonstrate, in higher magnification, the differences in ultrastructures between these three groups.

It is interesting to also note that glycogen rosettes did not demonstrate any appreciable quantitative or qualitative change in any of the groups.

TABLE 6. *Effect of Protein Repletion on Serum Globulins*

Group	Diet	Alpha 1	Alpha 2	Beta	Gamma
II	Protein-	.66	.50	118	.62
	free	.84 ± .10	.42 ± .13	.81 ± .10	.49 ± .13
III	TPN	**	*	*	*
		.65 ± .11	.58 ± .22	1.06 ± .29	.36 ± .09
Mean percentage change		23% ↓ .87	38% ↑ .65	31% ↑ 1.30	27% ↓ .50

* p < .05.
** p < .001.



FIGS. 2a–c. (a, top) Liver of control rat. (H & E, ×160) (b, center) Liver of protein depleted control showing marked fatty infiltration (H & E, ×160) (c, bottom) Liver following TPN repletion showing complete reversal of fatty change. (H & E, ×160).

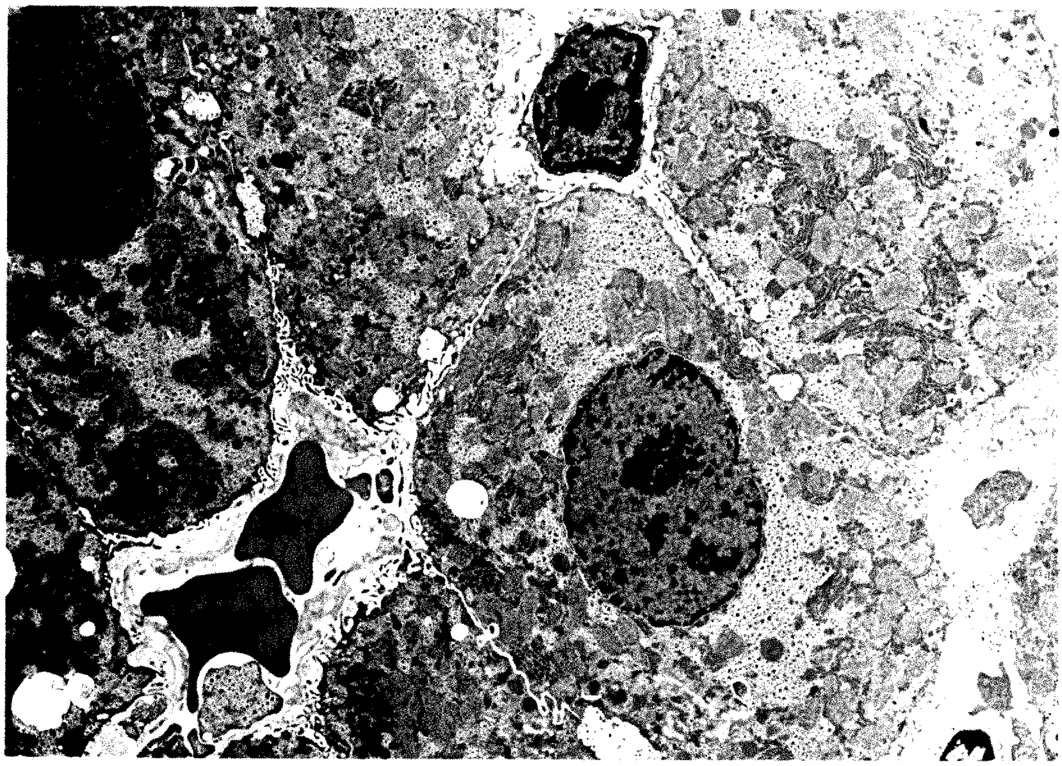


FIG. 3a. Ultrastructure of control rat liver. Note the abundant parallel strands of rough endoplasmic reticulum (rer) in close association with the mitochondria (×7,020).

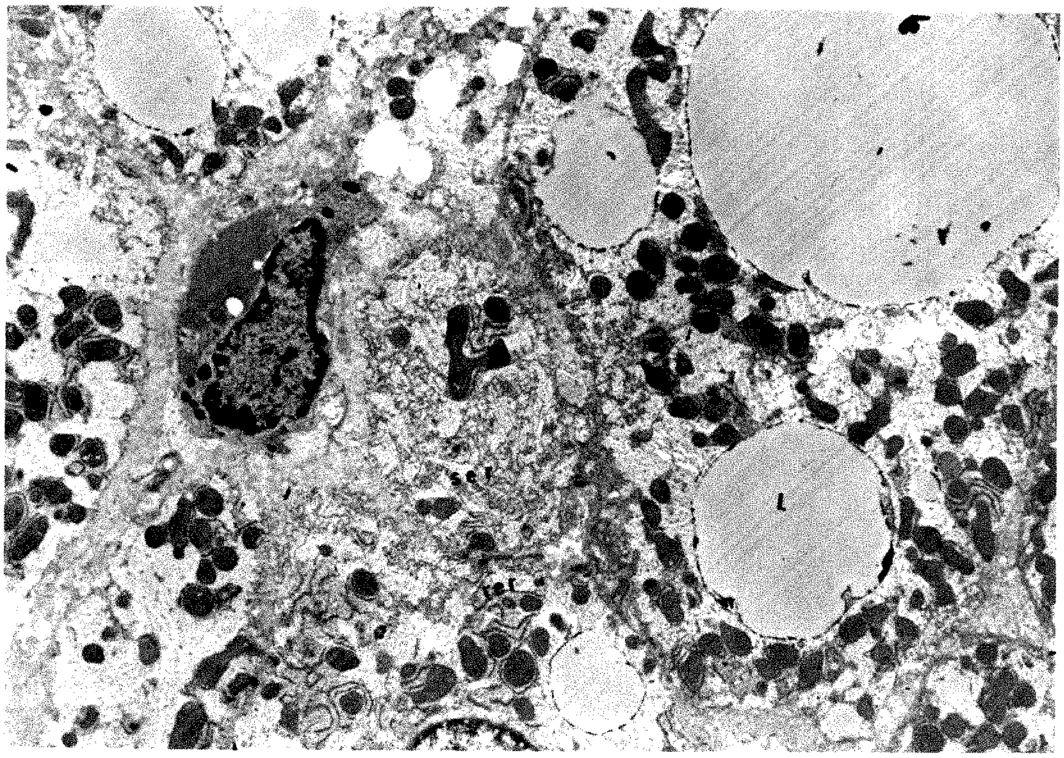


FIG. 3b. Ultrastructure of protein depleted control showing large intracytoplasmic lipid droplets (L), marked proliferation of smooth endoplasmic reticulum (ser) and reduction of rough endoplasmic reticulum (rer) (×7,020).

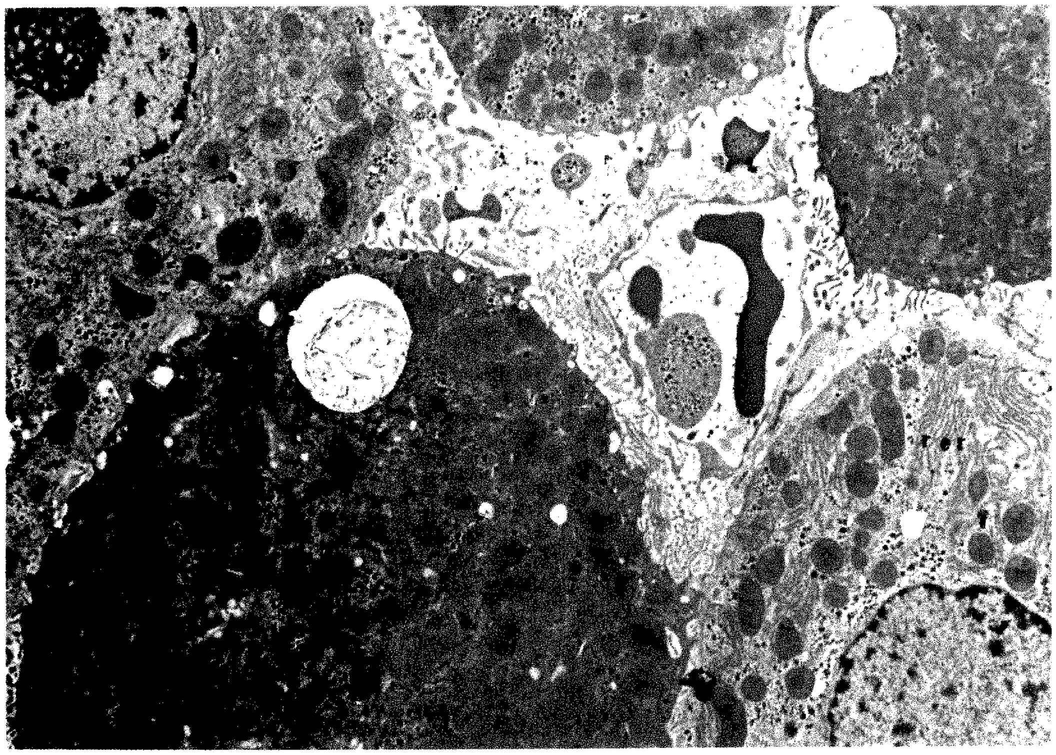


FIG. 3c. Ultrastructure of rat liver following TPN repletion. Note the disappearance of ser and increase in the rer comparable in amount to the control (×7,020).

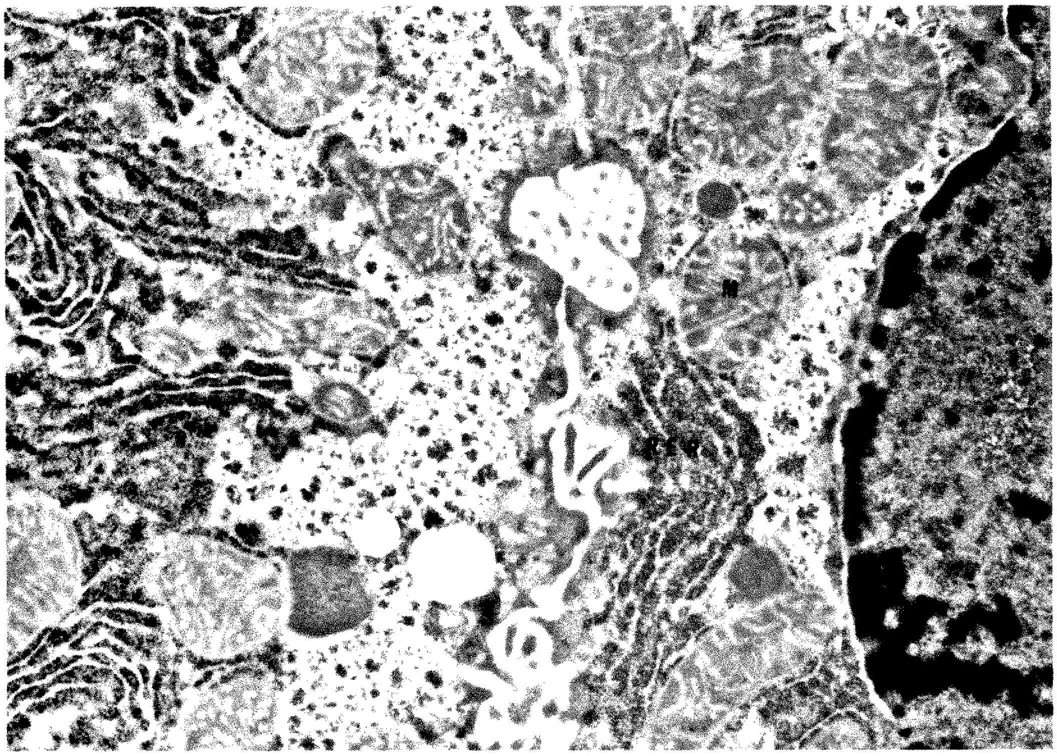


FIG. 4a. Higher magnification of ultrastructure of control rat liver. RER = Rough Endoplasmic Reticulum. M = Mitochondria (×29,700).

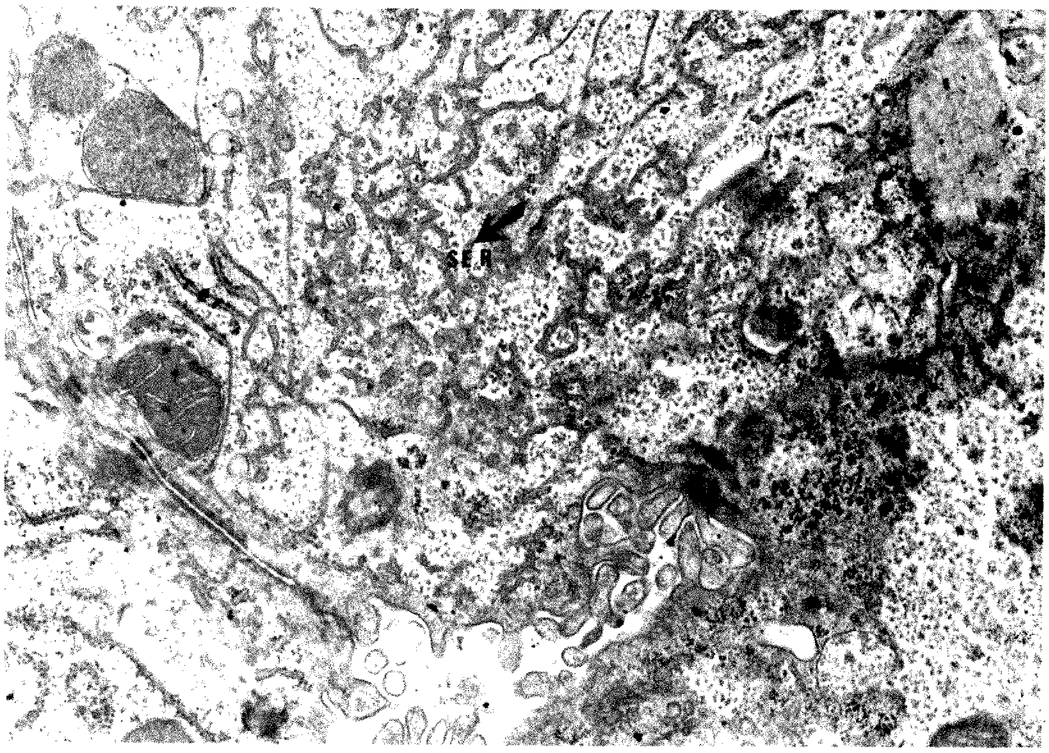


FIG. 4b. Higher Magnification of protein depleted control ultrastructure. Note the meshwork of fine branching SER.

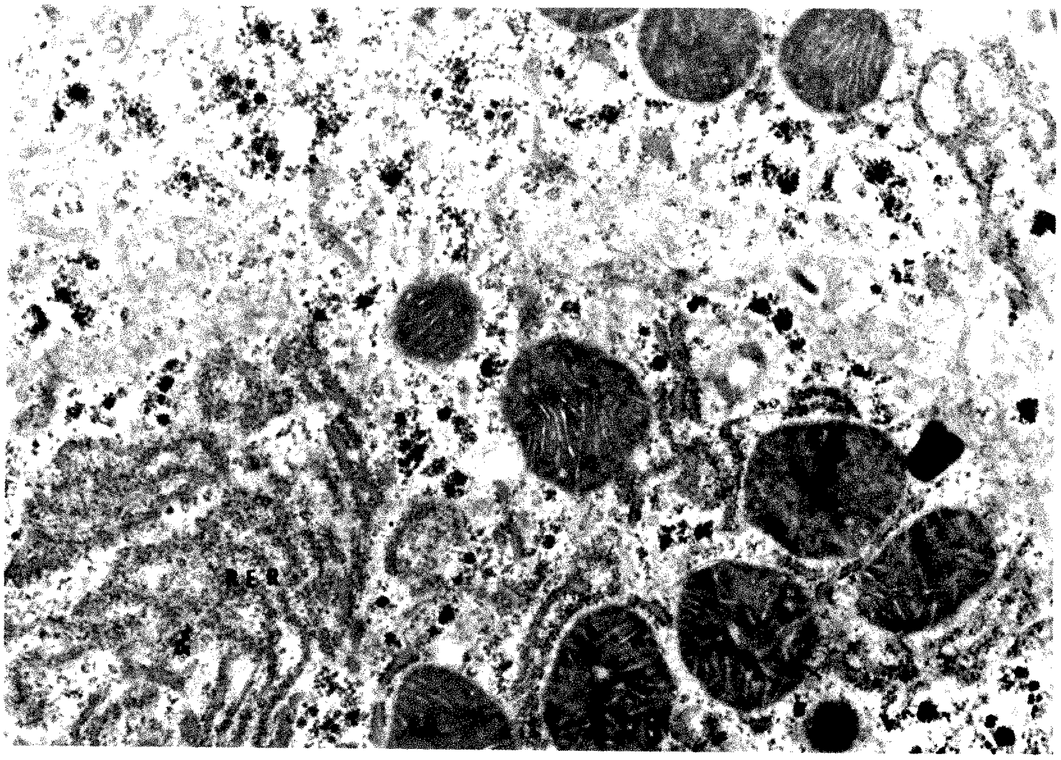


FIG. 4c. Higher magnification of TPN repletion rat liver showing normal ultrastructure (×29,700).

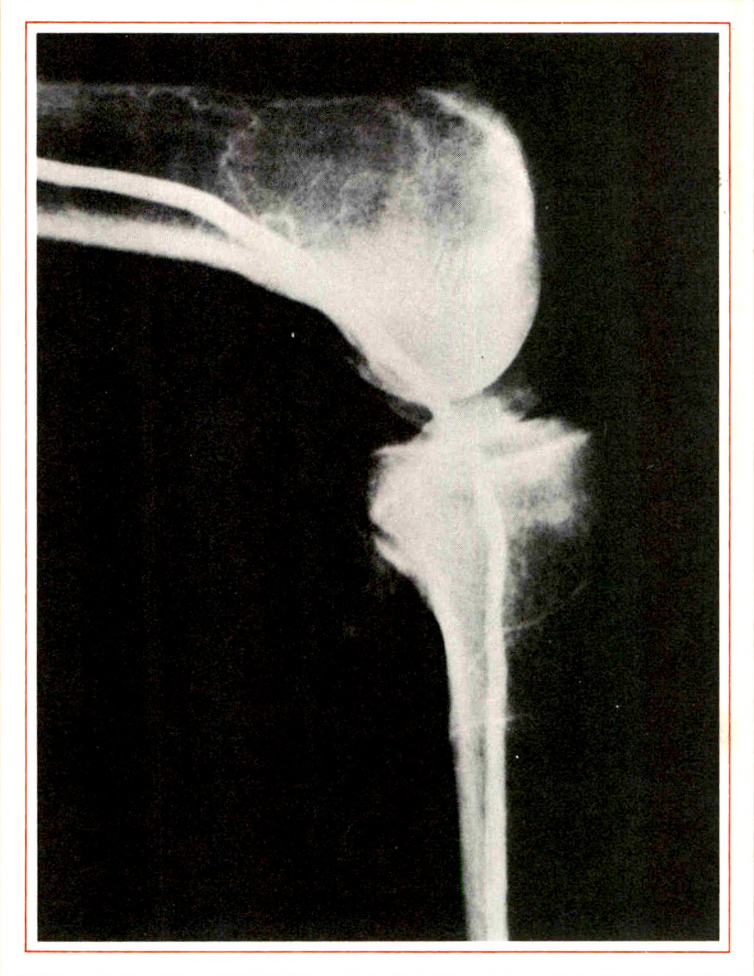
Discussion

Protein–calorie malnutrition or marasmus is accompanied by weight loss that is generalized and has no specific associated hepatic cellular abnormality. Relatively isolated protein deficiencies with an adequate or near adequate intake of calories, or kwashiorkor, is associated with weight loss, marked accumulation of intrahepatic fat, and hypoalbuminemia.[2] In this experiment, protein deficiency caused a more marked reduction in liver nitrogen content than body or liver weight loss or lowered albumin levels. A typical pattern of decreased beta and gamma globulins and an increased level of alpha I globulins accompany this dietary induced protein deficiency. Morphologically, a large accumulation of intrahepatic fat, shown in previous experiments to be triglycerides predominantly,[6] occurred as well as a decrease in hepatic rough endoplasmic reticulum. All of these changes reverted to normal after seven days of total parenteral nutrition, except for the gamma globulin level. The reason for this is not apparent at present, but continuing work is being carried on to try to delineate this problem. Also, the etiologic factors of the increased SER in the livers of protein depleted rats is not known. The SER is associated with cholesterol metabolism and storage and bile acid synthesis.[5] The ability of drugs to cause dramatic changes in the proportion of SER and RER in the liver and a four fold increase in the amount of cholesterol synthesis has also been well documented. The increase in SER in protein depleted rats needs further delineation.

References

1. Hambraeus, L., Forsum, E., Abrahamsson, L. and Lönnerdal, B: Automatic Total Nitrogen Analysis in Nutritional Evaluations Using a Blocks Digester. Anal. Biochem. 72:78–85, 1976.
2. Bistrian, B. R., Sherman, M., Blackburn, G. L., et al.: Cellular Immunity in Adult Marasmus. Arch. Int. Med., 137:1408, 1977.
3. Chaney, A. L.: A New Time Saving Method of Determining Nitrogen in Biological Material. Clin. Chem., 14:615, 1968.
4. Faulk, W. P., Demaeyer, E. M. and David, A. J. S.: Some Effects of Malnutrition on the Immune Response in Man. Am. J. Clin. Nutr., 27:638, 1974.
5. Jones, A. L. and Fawcett, D. W.: Hypertrophy of the Agranular Endoplasmic Reticulum in Hamster Liver Induced by Phenobarbital. J. Histochem. Cytochem., 14(3):215, 1966.
6. Madi, K., Jervis, H. R., Anderson, P. R. and Zimmerman, M. R.: A Protein Deficient Diet. Effect on Liver, Pancreas, Stomach and Small Intestine of the Rat. Arch. Pathol., 89:38, 1970.
7. Steiger, E., Daly, J. M., Allen, T. R., Dudrick, S. J., Vaus, H. M.: Postoperative Intravenous Nutrition. Effects on Body Weight, Protein Regeneration, Wound Healing and Liver Morphology. Surgery, 73(5):686, 1973.
8. Steiger, E., Naito, H. K., Cooperman, A. M. and O'Neill, M.: Effect of Lipid Calories on Weight Gain, Nitrogen Balance, Liver Weight and Composition in Total Parenteral Nutrition (TPN). Surg. Forum, 28:83, 1977.
9. Steiger, E., Vars, H. M. and Dudrick, J.: A Technique for Long-term Intravenous Feeding in Unrestrained Rats. Arch. Surg., 104:330, 1972.

GORE-TEX® reinforced vascular grafts, after 60,000 implants:



What we've learned.

Summary of Clinical Data, as of September 25, 1978.

Operation type	Number Implanted	Number Patent	% Patency	Avg. Months Weighted Experience	Months Maximum Experience
Above-Knee					
Fem-pop	1740	1526	88%	3.6	34
Ilio-fem	153	145	95%	4.1	22
Ilio-pop	58	54	93%	2.1	18
Fem-fem	105	98	93%	2.3	20
Pop-segmtl	14	11	79%	1.3	17
Aorta-pop	21	16	76%	2.4	14
Aorta-fem	133	128	96%	6.4	29
Axil-fem	143	132	92%	1.7	14
Axil-bifem	31	31	100%	3.7	16
Aorto-iliac	5	5	100%	2.0	6
Fem-profunda	14	11	79%	1.9	15
Axil-pop	19	17	89%	5.5	16
Iliac-fem	2	1	50%	3.5	7
Iliac-pop	10	7	70%	6.0	24
Others	4	2	50%	<0.5	1
Group Totals	2452	2184	89%	3.6	34
Below-Knee					
Fem-dist-pop	958	792	83%	3.2	34
Fem-ant-tibial	183	129	70%	1.5	19
Fem-post-tibial	292	197	67%	2.6	38
Fem-peroneal	111	78	70%	1.7	22
Aorta-ant-tib	2	1	50%	0.0	0
Ileo-post-tib	5	4	80%	1.2	6
Ileo-pop	5	3	60%	3.0	5
Fem-dorsalis ped	24	13	54%	3.0	12
Aorto-dist pop	5	5	100%	4.8	7
Iliac ant-tib	4	4	100%	3.2	8
Axil-dist-pop	2	2	100%	11.0	13
Iliac-dist-pop	4	2	50%	0.5	1
Pop-post-tib	2	2	100%	0.5	1
Other	7	3	43%	<0.5	1
Group Totals	1604	1235	77%	2.8	38
Cross-over Grafts					
Fem-fem	185	176	95%	6.2	30
Fem-pop	37	33	89%	2.2	24
Fem-profunda fem	3	3	100%	2.3	7
Axil-fem	6	6	100%	3.0	16
Fem-distal pop	1	1	100%	7.0	7
Others	4	3	75%	<0.5	2
Group Totals	236	222	94%	5.4	30
Composite Grafts					
C-fem-distal-pop	9	9	100%	2.6	8
C-fem-ant-tib	3	3	100%	6.0	7
C-fem-post-tib	14	13	93%	3.6	7
C-fem-peroneal	4	4	100%	2.5	5
Group Totals	30	29	97%	3.4	8
AV Fistulae	496	416	84%	3.2	22
Forearm	504	478	95%	0.8	18
Upper arm	370	352	95%	3.6	20
Arm	49	39	80%	0.7	10
Leg	101	98	97%	1.0	18
Group Totals	1520	1383	91%	2.3	22
Pulmonary Grafts					
Aorta-pulm shunt	57	48	84%	3.4	27
Pulm reconstrts	3	2	67%	0.0	0
Subclav-pulm	1	1	100%	1.0	1
Group Totals	61	51	84%	3.1	27
Other Arterial Grafts					
Renal artery	18	17	94%	10.7	30
Axil-axil	33	33	100%	4.1	18
Carot-subclav	52	50	96%	8.9	31
Aorto-coronary	15	11	73%	2.3	17
Aorto-renal	25	23	92%	4.0	26
Others	64	62	97%	3.2	29
Group Totals	207	196	95%	5.5	31
Venous Grafts	38	34	89%	7.8	42
Patches	143	135	94%	5.0	30
Totals, All Operations	6291	5469	87%	3.2	42

In 1977, we said: "It is time to consider GORE-TEX reinforced polytetrafluoroethylene (PTFE) vascular grafts as a viable alternative to saphenous vein autografts."

Has experience borne out that claim? Let's take another look.

The GORE-TEX® reinforced PTFE graft works.

If anecdotes were data, we'd have no trouble proving this point. Most surgeons who have used our grafts are high in their praise.

It is, in the majority opinion, the first such graft to come close to the promises made for it.

It is, according to observations and recent *in vitro* studies, relatively thromboresistant. And, when a thrombus forms, it is easy to de-clot.

It is, according to theory but not yet confirmed by data, less likely to present embolism problems later. (A thin, stable intima forms. Whether it's a neointima, pseudointima, or true endothelium is open to debate—but the thinness is the key to logic of the theory.)

It is, in its reinforced form, much more resistant than other versions of expanded PTFE to aneurysmal dilatation. It has high radial or bursting strength and high suture-holding power.

And it is easy to handle and use. Unlike woven or knitted grafts, it will not ravel or fray. And it does not require pre-clotting.

But is it, as we stated earlier, a viable alternative to the saphenous vein?

Yes, *if*.

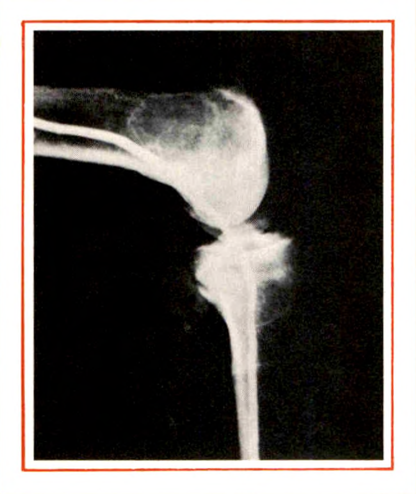
Yes, *if* there is no vein available.

Yes, *if* the vein is "borderline," either in size or condition.

Yes, *if* the patient's condition is such that a prolonged exposure to anaesthesia, or even to the delay in providing the vein, is critical.

Yes, *if* there is the likelihood of cardiac surgery, for which the saphenous vein should be saved.

Given those indications, the GORE-TEX graft is, indeed, a viable alternative to the saphenous vein. But unless those conditions exist, prudence and experience make the saphenous vein the graft of choice.



Arteriogram of a GORE-TEX polytetrafluoroethylene graft during flexion of the knee.

The problem of proof.

As of September 25, 1978, there were approximately 60,000 GORE-TEX vascular graft implants, with over 6,000 follow ups. The overall patency rate was 87%.

Those data, sliced into what we hope are useful pieces, are presented in Table at left.

A close look at the data will reveal one problem: average follow-up times.

They're too short.

The problem is two-fold.

First, we are, of course, dependent on the voluntary cooperation of surgeons for our follow-up data. And we know that if you were to provide all the data that all manufacturers wanted, you would have to spend all of your hours filling out follow-up forms. And, of course, even if you had the time, you can't keep up with all patients over a period of years.

The second part of the problem is statistical. The use of GORE-TEX grafts is increasing so rapidly that we will, for a long time to come, have a far greater number of recent implants than of old ones. (For every GORE-TEX graft implant used three years ago, there are almost 100 used today. Our current reported rate-of-use is approximately 5,000 per month.)

This necessarily skews our data average toward the more recent history. Which is also true for a life table method of data presentation. Even though the maximum experience reported in each category is in the two-to-three *year* range, the weighted averages are more like two-to-three *months.*

More data. More problems. Some suggestions.

On the last page of this advertisement, you'll find a bibliography of published experimental and clinical reports on the use of GORE-TEX vascular grafts, and a coupon for your convenient use.

One problem is that we know the list is not current. Additional papers are always being delivered, and published. If you would like us to keep you up-to-date as new reports appear, check the appropriate box on the coupon.

A more basic problem with these data, and ours, and *all* vascular statistics is the lack of uniformity in reporting. We're supporting efforts to establish some profession-wide protocols begun with a symposium at the 1978 meeting of the American College of Surgeons. If you have any suggestions at all, we'd appreciate them. Just write to us.

GORE-TEX® vascular grafts, in brief.

GORE-TEX vascular grafts are made of expanded, low-density polytetrafluoroethylene (PTFE), reinforced by a strong, fine lattice of the same material wound about the exterior.

GORE-TEX vascular grafts are easy to handle, with excellent resistance to kinking. And they exhibit high suture-holding power. They are, of course, fully biocompatible and, unlike knitted or woven prostheses, do not require pre-clotting.

GORE-TEX vascular grafts for vascular surgery are available in a wide range of diameters.

See next page for free GORE-TEX graft test-pack and complete bibliography, available as reprints.

Free test-pack, reprints.

Submit the handling and suture-holding characteristics of GORE-TEX grafts to the most meaningful test equipment: your own hands. Our test kit, not intended for actual surgery, includes a short length of a GORE-TEX graft and a 6-0 double-armed suture. Try it for yourself. Also, take your choice of reprints of any of the experimental, clinical, and engineering reports listed.

Current bibliography.

1. **Nonvein Bypass in Below-Knee Reoperation for Lower Limb Ischemia** Steven J. Burnham, M.D., D. Preston Flanigan, M.D., James J. Goodreau, M.D., James S. T. Yao, M.D., Ph.D., and John J. Bergan, M.D., Chicago, Ill. *Surgery,* Sept., 1978

2. **Expanded Polytetrafluoroethylene as Dialysis Access Grafts: Serial study of Histology and Fibrinolytic activity** R. Shack, M.D., W. Neblett, M.D., R. Richie, M.D., R. Dean, M.D. *The American Surgeon* Dec. 1977 .

3. **A Prosthesis For Blood Access In Patients with Thrombosis of Peripheral Vasculature** T. Buselmeir, M.D., J. Rynasiewicz, M.D., D. Sutherland, M.D., R. Howard, M.D., T. Davin, M.D., S. Mauer, M.D., R. Simmons, M.D., J. Najarian, M.D., C. Kjellstrand, M.D. *Dialysis and Transplantation* August 1977

4. **A Synthetic Vascular Conduit (Expanded PTFE) For Hemodialysis Access—A Preliminary Report** B. Pasternak, M.D., S. Paruk, M.D., S. Kogan, M.D., S. Levitt, M.D. *Vascular Surgery* Mar/April 1977

5. **Polytetrafluoroethylene Grafts for Arteriovenous Fistulae** A. Mohaideen, M.D., M. Avram, M.D., R. Mainzer, M.D. *N.Y. State Journal of Medicine* Dec., 1976

6. **Arterial Prosthesis of Microporous Expanded Polytetrafluoroethylene for Construction of Aorta-Pulmonary Shunts** A. Gazzaniga, M.D., J. Lamberti, M.D., R. Siewers, M.D., D. Sperling, M.D., W. Dietrick, M.D., R. Arcilla, M.D., R. Replogle, M.D. *Journal of Thoracic and Cardiovascular Surgery* Sept., 1976

7. **The Use of Expanded Microporous Polytetrafluoroethylene for Limb Salvage: A Preliminary Report** C. Campbell, M.D., D. Brooks, M.D., M. Webster, M.D., H. Bahnson, M.D. *Surgery* May, 1976

8. **Small-Vessel Replacement with GORE-TEX (Expanded Polytetrafluoroethylene)** A. Florian, M.D., L. Cohn, M.D., G. Dammin, M.D., J. Collins, M.D. *Archives of Surgery* March, 1976

9. **A Small Arterial Substitute: Expanded Microporous Polytetrafluoroethylene: Patency Versus Porosity** C. Campbell, M.D., D. Goldfarb, M.D., R. Roe, M.D. *Annals of Surgery* August, 1975

10. **Segmental Venous Replacement** D. Smith, Lt. Cmdr. (MC) USN, J. Hammon, M.D., J. Anane-Sefah, M.D., R. Richardson, M.D., C. Trimble, M.D. *Journal of Thoracic and Cardiovascular Surgery* April, 1975

11. **Replacement of Portal Vein During Pancreatectomy for Carcinoma** L. Norton, M.D., B. Eiseman, M.D. *Surgery* February, 1975

12. **Use of GORE-TEX Grafts for Replacement of the Superior and Inferior Venae Cavae** Y. Fujiwara, M.D., J. Cohn, M.D., D. Adams, M.D., J. Collins, M.D. *Journal of Thoracic and Cardiovascular Surgery* May, 1974

13. **A New Vascular Prosthesis for Small Caliber Artery** H. Matsumoto, M.D., T. Hasegawa, M.D., K. Fuse, M.D., M. Yamamoto, M.D., M. Saigusa, M.D. *Surgery* October, 1973

14. **A New Venous Prosthesis** T. Soyer, M.D., M. Lempinen, M.D., P. Cooper, L. Norton, M.D., B. Eiseman, M.D. *Surgery* December, 1972

15. **Summary of Clinical Evaluation Data,** May, 1977 *W. L. Gore & Associates, Inc.*

16. **Long-Term Dilatation Characteristics of GORE-TEX Vascular Grafts: Design Criteria** *W. L. Gore & Associates, Inc.*

Indications and Contraindications.

To sterilize:
Grafts may be sterilized using steam, gas or flash autoclave techniques. Remove the graft from the PVC blister tray and repackage for sterilization. Do not place the package label in contact with the graft during sterilization. Do not place objects on the repackaged graft during sterilization. (See Contraindication #5, 6)

Using steam, autoclave at or above these minimum requirements: 250° Fahrenheit (121° Centigrade) for 20 minutes at 15 p.s.i. Grafts should never be exposed to temperatures greater than 482° Fahrenheit (250° Centigrade).

Using a flash cycle, sterilize at or above these standard minimum requirements: 270° Fahrenheit (132° Centigrade) for 3 minutes at 30 p.s.i. Grafts should never be exposed to temperatures greater than 482° Fahrenheit (250° Centigrade).

Using gas, sterilize according to equipment instructions.

Indications:

1. Use a 5-0 or 6-0 nonabsorbable suture with a cardiovascular needle for best results on graft diameters of 6mm or less. Larger sutures may be used with larger diameter grafts.
2. Intra-operative inspection of anastomoses using irrigant solutions may result in serum leakage when blood flow is established in the graft. To prevent this, care must be taken not to generate syringe pressures sufficient to force irrigant through the graft walls. To do so will alter the hydrophobic (non-wetting) properties of GORE-TEX. (See Contraindication #11)
3. Trim grafts to desired length using sharp surgical instruments. Grafts should be handled with clean forceps or gloves. GORE-TEX grafts are not "elastic." Therefore, proper matching of lengths is essential. If the graft is cut too short, excessive stress may be placed on the sutures and the graft at the anastomosis. (See Contraindication #10)
4. Ensure, when using this graft in blood access applications or where repeated needle punctures of the graft are necessary, that needle puncture sites are spaced apart along the accessible sub-cutaneous length of the graft. Repeated needle puncture of the graft at the same site, or within the same immediate area, may cause mechanical damage to the graft which could lead to hematoma, false aneurysm or true aneurysm. Patients should be carefully monitored to assure that this instruction is followed.

Contraindications:

1. Do not pre-clot the graft.
2. Do not sterilize by irradiation techniques.
3. Grafts should never be exposed to temperatures exceeding 482° Fahrenheit (250° Centigrade).
4. Do not sterilize more than three times.
5. During sterilization, do not place grafts under heavy or sharp objects which might crush the grafts.
6. Do not attempt to sterilize the label attached to the PVC blister tray at high temperatures, as the materials (inks and adhesives) on the label may contaminate any objects in contact with the label during the sterilization cycle.
7. Do not handle graft with ungloved hands. It should be handled only with clean instruments.
8. Do not attempt to resterilize any unused graft portion which has been contaminated with blood or any other foreign material.
9. Do not use absorbable sutures.
10. Do not cut graft while holding under tension. Doing so may cause separation of the outer layer. The GORE-TEX graft is a composite structure consisting of an inner base tube and a thin outer layer which reinforces the base tube to prevent aneurysmal dilatation. Do not use any portion of a GORE-TEX graft which has damage to or separation of the outer layer of the graft.

    Should the outer reinforcing layer become frayed at the end of the graft, do not pull on or peel the outer layer from the base tube. Carefully trim off the portion of the graft where the outer layer is frayed.
11. Do not force irrigating solutions through the graft wall. Doing so may result in serum leakage after blood flow is established.
12. Do not place grafts in any fluid prior to use. Doing so may result in serum leakage after blood flow is established.
13. Do not puncture the graft repeatedly at the same site, or within the same immediate area. (See Indication #4)

CHIEF OF SURGERY

Grady Memorial Hospital (Emory University School of Medicine) is seeking applicants for the position of full-time **Chief of Surgery**. Applicant should be an experienced, board-certified surgeon with leadership ability and a background in administration, patient care, and teaching. Grady Hospital is an active inner-city, 964-bed hospital with heavy emphasis on trauma and acute medical emergencies. A total of 119 house staff (64 in General Surgery and 55 surgical specialists) and 220 medical students are assigned to the surgical services during a given academic year. The position includes a full-time academic appointment with Emory University School of Medicine and salary and benefits commensurate with background and experience. Individuals wishing to be considered for the position should send CV, list of publications, and names of references to:

George T. Tindall, M.D., Chairman
Grady Chief of Surgery Search Committee
1365 Clifton Road, N.E.
Atlanta, GA 30322

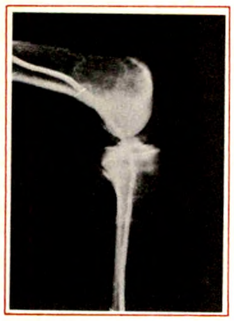
Closing date for receipt of applications—October 1, 1979. Women and minorities are encouraged to apply. Grady Memorial Hospital and Emory University are Affirmative Action/Equal Opportunity Employers.

MARYLAND GENERAL HOSPITAL

Surgical Education Director wanted for a 400-bed, University affiliated teaching hospital with residencies in General Surgery, Internal Medicine, Ophthalmology, OB/Gyn and Pathology. Salary negotiable, fringe benefits excellent. Must be Board Certified in general and vascular or thoracic surgery. Send curriculum vitae to:

Salvatore R. Donohue
Medical Director
Maryland General Hospital
827 Linden Avenue
Baltimore, MD 21201

GORE-TEX® reinforced vascular grafts.



W. L. Gore & Associates, Inc.
P.O. Box 1220
Route 213 North
Elkton, MD 21921

Gentlemen:

☐ Please send me your GORE-TEX vascular graft test kit.

☐ Please send me the reprints and reports whose numbers I have circled.

1. 3. 5. 7. 9. 11. 13. 15.
2. 4. 6. 8. 10. 12. 14. 16.

☐ Please send me additional reprints as they are published.

☐ Please have your representative call for an appointment.

☐ Enclosed are my suggestions for standardization of vascular statistics.

Name

Address

City State Zip

Hospital Affiliation

Surgical Specialty

THE CEPHALOSPORIN COST CONTAINMENT CALCULATOR.

"The determination as t[illegible] turned out to be almo[illegible] the basis of cost. Ce[illegible] be considered identica[illegible] i.e., therapeutic equi[illegible] terms of therapeutic e[illegible] two compounds are a[illegible]

—Richard Quintiliani, M.D.
Director, Division of Infectious Diseases
Hartford Hospital[1]

*Cephapirin, cephalothin and cefazolin are not chemically or generically equivalent and any statements made comparing these products are valid only when considering mutually approved indications.

Cephalosporins account for 39% of all hospital parenteral antibiotic purchases. That's a lot of cost to contain. But the potential for savings is great.

And, the only machine you'll ever need to calculate maximum cephalosporin savings is already on your desk.

For specific details on how Cefadyl can save money for your institution, just pick up your telephone and dial one of the toll-free numbers listed below.

Everyone talks about hospital cost containment. But Bristol Laboratories has a cephalosporin price worth talking about!

Call the Cefadyl Cost Containment Hotline today–

In the Continental U.S.,
call toll-free

800-448-5779

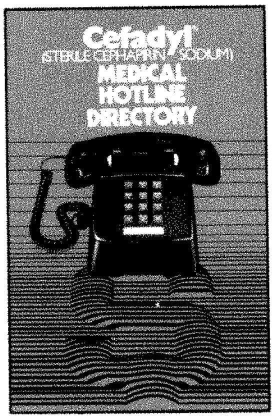
(In New York State, call toll-free 800-962-5746)

Cefadyl®
(STERILE CEPHAPIRIN SODIUM)
can save money!

SEE NEXT PAGE FOR PRESCRIBING INFORMATION

Connect yourself to the Cefadyl® (STERILE CEPHAPIRIN SODIUM) MEDICAL HOTLINE–FREE!

The Cefadyl Medical Hotline Directory lists all the government agencies and private institutions that affect the practice of medicine in America today. And, for most listings, the Directory includes names and numbers of the key individuals, not just a general switchboard.



To obtain your free copy of the Cefadyl Medical Hotline Directory, just call toll-free
800-448-5779
in Continental U.S.
(New York State residents call toll-free
800-962-5746).

Cefadyl® (STERILE CEPHAPIRIN SODIUM) can save money!

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CEFADYL®
(sterile cephapirin sodium)
(7) Cefadyl 3/6/78

For complete prescribing information, please consult the Official Package Circular.

Contraindications

Cefadyl (sterile cephapirin sodium) is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

Warnings

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs,should receive antibiotics cautiously and then only when absolutely necessary. No exceptions should be made with regard to Cefadyl.

If an allergic or anaphylactic reaction should occur, discontinue Cefadyl and institute appropriate treatment.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions

The renal status of the patients should be determined prior to and during Cefadyl therapy, since in patients with impaired renal function, a reduced dose may be appropriate.

Prolonged use of Cefadyl may result in the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken. With high urine concentrations of cephapirin, false-positive glucose reactions may occur if Clinitest, Benedict's Solution or Fehling's Solution are used. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Tes-Tape) be used.

Adverse Reactions

Hypersensitivity — Cephalosporins were reported to produce the following reactions: maculopapular rash, urticaria, reactions resembling serum sickness, and anaphylaxis. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—During large-scale clinical trials, rare instances of neutropenia, leukopenia, anemia were reported. Some individuals, particularly those with azotemia, have developed positive direct Coombs' test during therapy with other cephalosporins.

Liver—Elevations in SGPT or SGOT, alkaline phosphatase, and bilirubin have been reported.

Kidney—Rises in BUN have been observed; their frequency increases in patients over 50 years old.

How Supplied

Cefadyl (sterile cephapirin sodium) for I.M. or I.V. Injection. Cephapirin sodium equivalent to 1 Gm., 2 Gm., 4 Gm., or 20 Gm. cephapirin. For information on package sizes available, refer to the current price schedule.

1. Quintiliani R: The Cephalosporins: An Overview, film, (Feb) 1979.

BRISTOL®
©1979 BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, N.Y. 13201

Because you need to know which patient is at risk of postoperative thrombosis...

ORTHO* Chromogenic Antithrombin III Assay

Available now for incorporation into your routine screening procedures, as:

- A presurgical screen for levels of Antithrombin III
- An adjunct to heparin monitoring procedures

ORTHO DIAGNOSTICS INC.
Raritan, New Jersey 08869

*Trademark © O.D. 1979

I am interested in Antithrombin III (AT III). Please send me:

☐ Selected reprints on the diagnostic utility of ORTHO* Chromogenic Antithrombin III Assay

☐ An informative brochure on AT III as an inhibitor and the principles of the ORTHO Chromogenic AT III Assay

Name ____________________

Address ____________________

City ____________ State ____________ Zip ____________

Your specialty ____________________

Who, in your hospital, establishes routine presurgical screening procedures ____________________

*Trademark

ORTHO

Viokase® costs your patients less than other pancreatic preparations

(Based upon Drug Topics Redbook 1979 published prices.)

4x N.F. Protease
6x N.F. Amylase
10 x N.F. Lipase
(whole pancreas)

Twenty-Five Year Veteran

in the management of exocrine pancreatic deficiencies

The effectiveness of Viokase is confirmed by over twenty-five years of clinical experience... and it still costs your patients less than other pancreatic preparations. Current literature[1,2] documents the use of Viokase as a digestive aid in cystic fibrosis and in exocrine pancreatic deficiencies usually due to chronic pancreatitis, pancreatectomy or obstruction in the pancreas caused by malignant growth.

VIOKASE®
(pancreatin)

Description: VIOKASE is a pancreatic enzyme concentrate of porcine origin containing standardized amylase, protease and lipase activities plus esterases, peptidases, nucleases and elastase.

The enzyme potency of the tablets and powder are:

	Each 325 mg. Tablet	Each 0.75 gram (⅓ teaspoonful)
Lipase, N.F. Units	6.500	15.000
Protease, N.F. Units	32.000	75.000
Amylase, N.F. Units	48.000	112.500

Under conditions of the N.F. test method (in vitro) VIOKASE has the following total digestive capacity:

	Each 325 mg. Tablet	Each 0.75 g. Powder
Dietary Fat	23	53 grams
Dietary Protein	32	75 grams
Dietary Starch	48	112 grams

VIOKASE Tablets are not enteric coated.

Indications: As a digestive aid in cystic fibrosis and in exocrine pancreatic deficiencies usually due to chronic pancreatitis, pancreatectomy or obstruction in the pancreas caused by malignant growth.

Administration and Dosage:
Powder: Dosage to patients with cystic fibrosis: ⅓ teaspoon (0.75 grams) with meals.

Tablets: Dosage to patients with cystic fibrosis or chronic pancreatitis —1 to 3 tablets with meals. For aiding digestion in patients with pancreatectomy or gastrectomy—1 to 2 tablets taken at 2-hour intervals, or as directed by physician.

Caution: Federal law prohibits dispensing without prescription.

Warnings: Avoid inhalation of powder.

Precautions: Use with caution in patients known to be allergic to pork protein.

How Supplied:
Powder: Bottles of 4 ounces and 8 ounces
Tablets: Bottles of 100 and 500

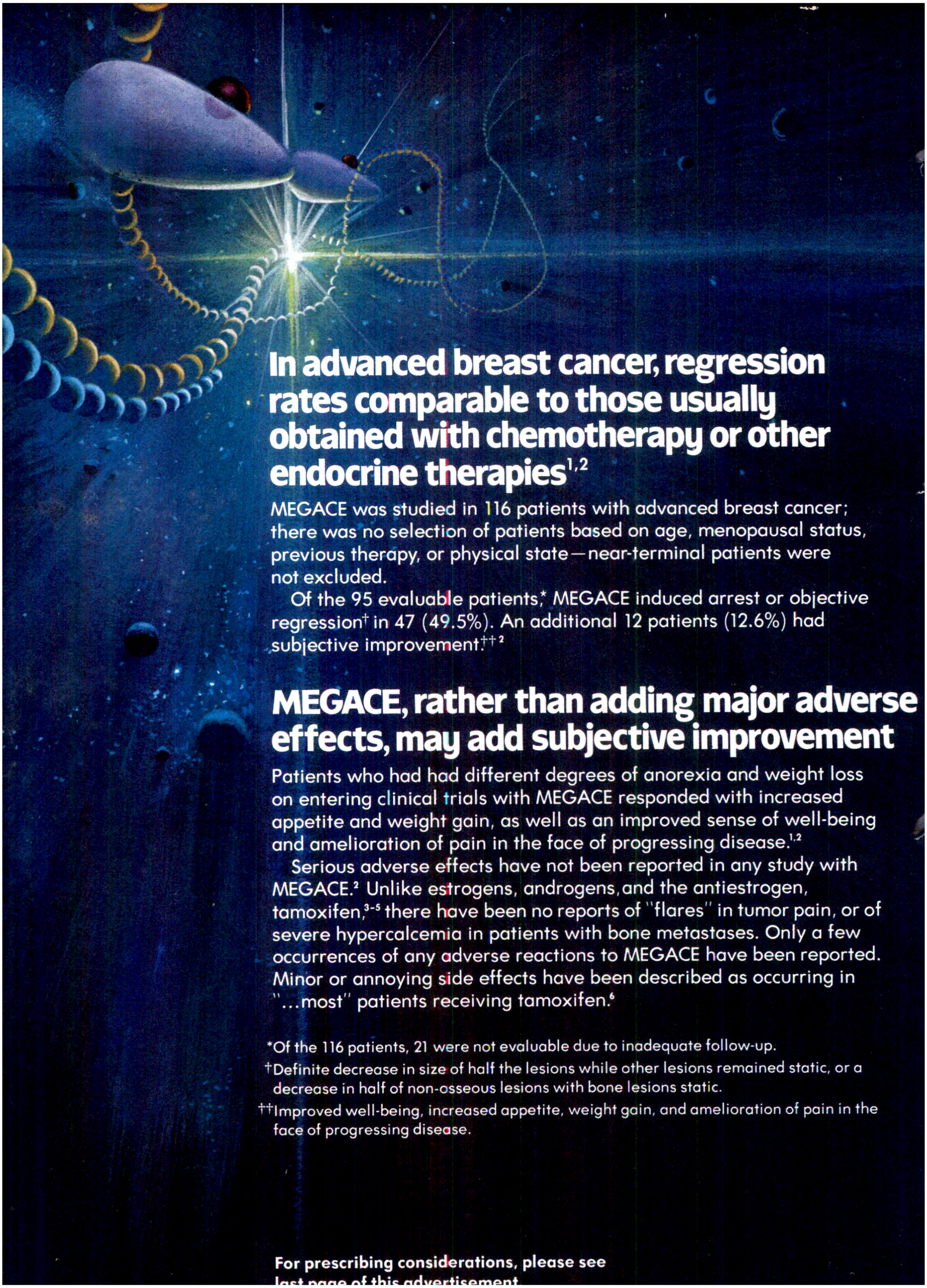
Literature Available: Complete literature available upon request including information on BEEF VIOKASE DERIVED FROM BEEF PANCREAS FOR THOSE EXCEPTIONAL PATIENTS ALLERGIC TO PORK.

1. Kafka, E. and Klaser, H.: "Pancreatic Disease", *Postgraduate Medicine*, 57: 140-145, 1975.
2. Long, W.B. and Weiss, J.B.: *Gastroenterology*, 67:920-925, 1974.

VIOBIN

VIOBIN CORPORATION
A Subsidiary of A.H. Robins Company
Monticello, IL 61856

in the progression of advanced breast cancer
your next therapeutic step may be the safest
TABLETS, 20 mg and 40 mg
MEGACE®
(MEGESTROL ACETATE)
antiestrogenic oral progestogen
For prescribing considerations, please see last page of this advertisement.



In advanced breast cancer, regression rates comparable to those usually obtained with chemotherapy or other endocrine therapies[1,2]

MEGACE was studied in 116 patients with advanced breast cancer; there was no selection of patients based on age, menopausal status, previous therapy, or physical state—near-terminal patients were not excluded.

Of the 95 evaluable patients,* MEGACE induced arrest or objective regression† in 47 (49.5%). An additional 12 patients (12.6%) had subjective improvement.††[2]

MEGACE, rather than adding major adverse effects, may add subjective improvement

Patients who had had different degrees of anorexia and weight loss on entering clinical trials with MEGACE responded with increased appetite and weight gain, as well as an improved sense of well-being and amelioration of pain in the face of progressing disease.[1,2]

Serious adverse effects have not been reported in any study with MEGACE.[2] Unlike estrogens, androgens, and the antiestrogen, tamoxifen,[3-5] there have been no reports of "flares" in tumor pain, or of severe hypercalcemia in patients with bone metastases. Only a few occurrences of any adverse reactions to MEGACE have been reported. Minor or annoying side effects have been described as occurring in "...most" patients receiving tamoxifen.[6]

*Of the 116 patients, 21 were not evaluable due to inadequate follow-up.

†Definite decrease in size of half the lesions while other lesions remained static, or a decrease in half of non-osseous lesions with bone lesions static.

††Improved well-being, increased appetite, weight gain, and amelioration of pain in the face of progressing disease.

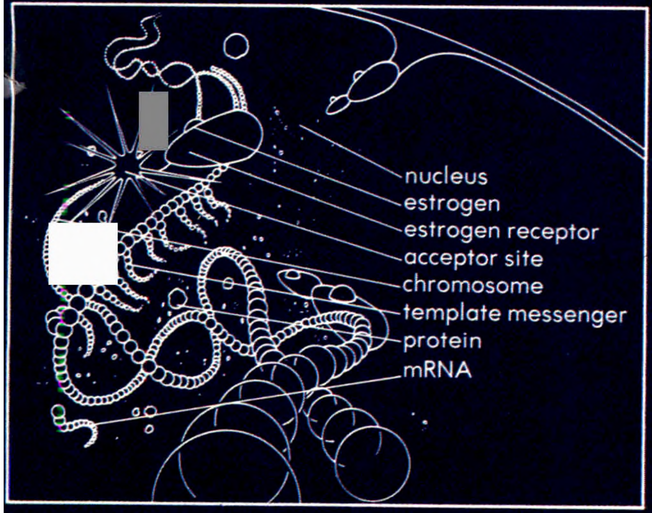
For prescribing considerations, please see last page of this advertisement.

MEGACE may help prolong the effectiveness of chemotherapy

In sequential, single, or combination therapy, a drug such as MEGACE—providing different biochemical mechanisms of action—may permit sequential use of chemotherapy by delaying or preventing acquisition of resistance by tumor cells to chemotherapeutic agents.[7] This is most important in continuing effective chemotherapy in responsive tumors.[4,6,8]

MEGACE may benefit patients at any sequence of therapy. Given after cytotoxic agents in patients with widespread metastases, MEGACE may provide remission rates comparable to those with cytotoxic therapy...plus, a respite from toxicity and time for bone marrow to recover.[1,9]

MEGACE is the only oral progestogen indicated for palliative treatment of both advanced breast and endometrial cancer



Estrogen activation of cell begins with hormone's passage into cytoplasm. This occurs with all cells, but in estrogen-sensitive cells the hormone is "attracted" by a specific protein receptor. Binding of the hormone to the receptor protein permits both to pass through the nuclear membrane and attach nonspecifically to chromatin. Hormone-receptor complex moves to a specific effector site on the chromosome, where it triggers synthesis of messenger RNA corresponding to the gene at the site. Final step is migration of mRNA to cytoplasm, where it presides over protein synthesis.*

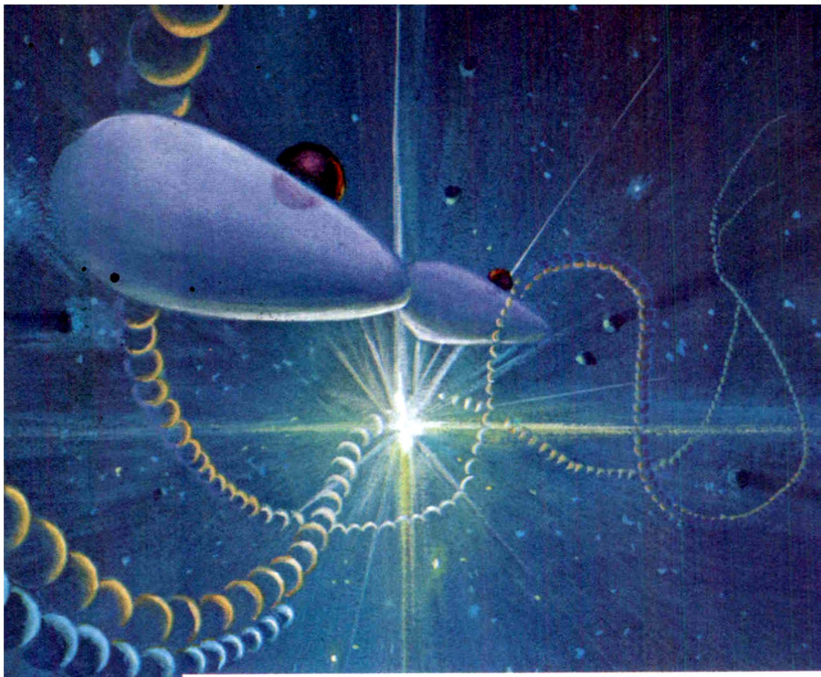
Adapted from O'Malley.[10]

TABLETS, 20 mg and 40 mg

MEGACE®

(MEGESTROL ACETATE)

Mead Johnson PHARMACEUTICAL DIVISION



TABLETS, 20 mg and 40 mg

MEGACE®

(MEGESTROL ACETATE)

Oral endocrine therapy in advanced breast cancer

May benefit patients objectively and subjectively, with unsurpassed safety

REFERENCES:

1. Ansfield FJ, Davis HL Jr, Ramirez G, et al: Further clinical studies with megestrol acetate in advanced breast cancer. *Cancer* 38:53, 1976.
2. Data on file, Mead Johnson Pharmaceutical Division.
3. Carter SK: What you can do for your patients with breast cancer. *Res Staff Phy* 25:56–64, 1979.
4. Legha SW, Davis HL, Muggia FM: Hormonal therapy of breast cancer: new approaches and concepts. *Ann Intern Med* 88:69–77, 1978.
5. Minton MJ, Cantwell BMJ, Knight RK, et al: Safety of tamoxifen. *Lancet* 1:396–397, 1978.
6. Heuson J-C: Current overview of EORTC clinical trials with tamoxifen. *Cancer Treat Rep* 60:1463–1466, 1976.
7. Canellos GP, DeViat VT, Gold GL, et al: Combination chemotherapy for advanced breast cancer: response and effect on survival. *Ann Intern Med* 84:389–392, 1976.
8. Lippman ME, Allegra JC: Current concepts in cancer: receptors in breast cancer. *New Eng J Med* 2:930–933, 1978.
9. Ansfield FJ, Davis HL Jr, Ellerby RA, Ramirez G: A clinical trial of megestrol acetate in advanced breast cancer. *Cancer* 33:907–910, 1974.
10. O'Malley BW: Hormones, genes, and cancer. *Hosp Pract* 10:65, 1965.

WARNING

THE USE OF PROGESTATIONAL AGENTS DURING THE FIRST FOUR MONTHS OF PREGNANCY IS NOT RECOMMENDED

Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion or treat threatened abortion. There is no adequate evidence that such use is effective and there is evidence of potential harm to the fetus when such drugs are given during the first four months of pregnancy.

Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion. Therefore, the use of such drugs during the first four months of pregnancy is not recommended.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[1-5] One study[4] estimated a 4.7-fold increased risk of limb reduction defects in infants exposed *in utero* to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 to 1,000.

If the patient is exposed to Megace during the first four months of pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus.

INDICATIONS

Megace (megestrol acetate) is indicated for the palliative treatment of advanced carcinoma of the breast or endometrium (i.e., recurrent, inoperable, or metastatic disease). It should not be used in lieu of currently accepted procedures such as surgery, radiation, etc.

CONTRAINDICATIONS

As a diagnostic test for pregnancy.

WARNINGS

Administration for up to 7 years of megestrol acetate to female dogs is associated with an increased incidence of both benign and malignant tumors of the breast. Comparable studies in rats and ongoing studies in monkeys are not associated with an increased incidence of tumors. The relationship of the dog tumors to humans is unknown but should be considered in assessing the benefit-to-risk ratio when prescribing Megace and in surveillance of patients on therapy.

The use of Megace (megestrol acetate) in other types of neoplastic disease is not recommended.

PRECAUTIONS

There are no specific precautions identified for the use of Megace (megestrol acetate) when used as recommended. Close, customary surveillance is indicated for any patient being treated for recurrent or metastatic cancer. Use with caution in patients with a history of thrombophlebitis.

ADVERSE REACTIONS

No untoward effects have been ascribed to Megace therapy. Reports have been received of patients developing carpal tunnel syndrome, deep vein thrombophlebitis and alopecia while taking megestrol acetate.

OVERDOSAGE

No serious side effects have resulted from studies involving Megace (megestrol acetate) administered in dosages as high as 800 mg/day.

DOSAGE AND ADMINISTRATION

Breast cancer: 160 mg/day (40 q.i.d.).

Endometrial carcinoma: 40-320 mg/day in divided doses.

At least two months of continuous treatment is considered an adequate period for determining the efficacy of Megace (megestrol acetate).

HOW SUPPLIED

Megace® is available as light blue, scored tablets containing 20 mg or 40 mg megestrol acetate in bottles of 100 tablets each.

NDC 0087-0595-01, 20 mg tablet	Bottles of 100
NDC 0087-0596-41, 40 mg tablet	Bottles of 100

References:

1. Gal I, Kirman B, Stern J: Hormonal pregnancy tests and congenital malformation. *Nature* 216:83, 1967.
2. Levy EP, Cohen A, Fraser FC: Hormone treatment during pregnancy and congenital heart defects. *Lancet* 1:611, 1973.
3. Nora J, Nora A: Birth defects and oral contraceptives. *Lancet* 1:941, 1973.
4. Janerich DT, Piper JM, Glebatis DM: Oral contraceptives and congenital limb-reduction defects. *New Eng J Med* 291:697, 1974.
5. Heinonen OP, Slone D, Monson RR, et al: Cardiovascular birth defects and antenatal exposure to female sex hormones. *New Eng J Med* 296:67, 1977.

Mead Johnson PHARMACEUTICAL DIVISION

© 1979 Mead Johnson & Company • Evansville, Indiana 47721 U.S.A. MJL 9-4440

Carcinoma of the Hepatic Hilus

Surgical Management and the Case for Resection

BERNARD LAUNOIS, M.D., JEAN-PIERRE CAMPION, M.D., PIERRE BRISSOT, M.D., MICHEL GOSSELIN, M.D.

Tumor resection for treatment of carcinoma of the hepatic hilus was preferred over routine palliative decompression at the University Hospital Center, Rennes, France, in 1974. Since then, resection has been performed on 18 patients. In seven of these patients resection proved impractical because of the extension of a neoplasm into the portal vein or liver, therefore palliative decompression was performed. In 11 patients (61%) tumor resection, followed by reconstruction of the biliary tree, was performed successfully. All the resected tumors were adenocarcinomas of the proximal bile ducts. Four patients had simple hepatic duct resection. In two patients duct resection was associated with right lobectomy, in three patients with left lobectomy, in one patient with segmentectomy, and in one patient with excision of the right branch of the hepatic artery. There were two postoperative deaths. The mean survival time for the remaining nine patients is 521 days. Five patients were alive in August 1978, at intervals ranging from 175 to 1180 days after resection. These results contrast favorably with those obtained between 1968 and 1973, during which period nine patients had palliative decompression, with three postoperative deaths and a mean survival time of 164 days for the remaining six patients.

From the Clinique Chirurgicale B,
Hopital de Pontchaillou, Centre Hospitalo-Universitaire
de Rennes, Rennes, France

THE MOST COMMON malignant tumors of the hepatic hilus are primary carcinomas of the proximal bile ducts. Generally originating at or near the junction of the common hepatic duct with the left and right main hepatic ducts, they grow slowly and invade more by direct local spread than by blood borne or lymph borne dissemination.[15] It had previously been thought that most were unresectable[1-4,11,13] and could be treated only by palliative decompression of the biliary tract. Palliative decompression has been achieved by intrahepatic biliary-intestinal anastomosis,[2-4,6,7,9-12,14,17-19] or by biliary tree cannulation with T or Y tubes or the transhepatic transtumoral U tube.[4,9,12,14,15,21,22] Radiotherapy, at times in association with the U-tube procedure, has also proved an effective palliative measure in selected cases.[13,21]

A more radical approach, aimed at a definitive cure, has, however, also been adopted. Since the successful resection of a carcinoma of the right hepatic duct by Brown in 1954,[5] resection of hepatic duct carcinoma, followed by reconstruction of the biliary tree and often combined with wide hepatic resection has been reported with increasing frequency.[1,2,9,12,13,15,19] Encouraging results after *en bloc* tumor resection have been reported by Longmire et al.[15] who, in addition to removing the tumor, also performed extended hepatic resection including segments of the adjacent hepatic inflow blood supply, and of Fortner et al.[9] who combined hepatic lobectomy or total hepatectomy and liver transplantation with tumor excision.

The purpose of this paper is to describe our experience in the surgical management of malignant tumors of the hepatic hilus, and to show how our approach to these lesions has evolved over the last ten and one-half years.

Materials and Methods

Patients

Twenty-nine patients, 11 men and 18 women, ranging in the age from 41 to 81 years (mean 62.2 ± 11.2 years) were operated on for malignant tumors of the hepatic hilus at our institution from January 1, 1968 through June 30, 1978.

All the patients were jaundiced. Fourteen had epigastric or subcostal pain, often coinciding with the onset of jaundice, and 20 had severe weight loss accompanied by deterioration of the general condition. Six patients had had operations on the biliary tract (cholecystectomy in two patients, cholecystectomy and Kehr drainage in two patients, and cholecystostomy in two

---

Reprint requests: Bernard Launois, M.D., Hopital de Pontchaillou, 35000 Rennes, France.
Submitted for publication: February 13, 1978.

0003-4932/79/0800/0151 $00.85 © J. B. Lippincott Company

patients) at intervals ranging from 32 to 292 days (mean 137.7 ± 104.5 days) before operation. In five patients the initial clinical examination revealed an enlarged gall bladder. The laboratory findings were those of cholestatic jaundice and, apart from raised serum levels of the transaminases, aspartate and alanine aminotransferase, in 21 patients, they contributed little to the diagnosis. Three patients had marked hypoalbuminemia and two patients had hypergammaglobulinemia.

Diagnosis

The diagnosis was made preoperatively in six patients: in two patients by retrograde cholangiography; in two patients by cholangiography with a Kehr drain or cholecystostomy sound inserted at a previous operation; and in two patients by transhepatic cholangiography with an Okuda needle. In the remaining 23 patients the diagnosis was made peroperatively by transhepatic cholangiography.

Operative Procedures

During the first six years (1968–73) of the study, no tumor resection in the hepatic hilus was attempted. Out of the ten patients treated during that period, nine had a palliative biliary–jejunal anastomosis to the bile duct of segment III,* and the tenth had an exploratory laparotomy only.

In 1974, in contrast, we adopted radical and potentially curative surgery as our systematic approach to this condition. Of 19 patients we have treated since that date, palliative biliary–jejunal anastomosis has been the preferred procedure in one patient. This was a double anastomosis, that is, left and right anastomoses to the same jejunal loop.

Radical tumor resection was planned in 18 patients and successfully accomplished in 11 patients (61%). The sites of the resected tumors had been shown roentgenologically to correspond to Bismuth and Corlette's[4] type I (situated at the main hepatic duct junction but not obstructing it) in five cases, type II (obstructing the main junction only) in three cases, and type III (obstructing both the main and a secondary junction) in three cases.

Data of the 11 successful resections are summarized in Table 1. In nine patients the entire main hepatic duct junction was excised. In two patients (5 and 6) the upper part of the junction was preserved. The *en bloc* resection was limited to the hepatic ducts in four patients (2, 6, 10, and 11), and was extended to include right hepatic lobectomy in two patients, left hepatic lobectomy in three patients, resection of segment IV in one patient (Fig. 1), and excision of the right branch of the hepatic artery in one patient. Cholecystectomy was performed in all the patients. Biliary reconstruction was accomplished by anastomosis to a Roux-en-Y jejunal loop at the following sites: upper part of the main hepatic duct junction—two patients; reconstructed main hepatic duct junction—three patients; left hepatic duct—two patients; right hepatic duct—one patient; left and right hepatic ducts—one patient; and paramedian and right lateral hepatic ducts—two patients. In three patients a transanastomotic tutor drain was used because of the precarious state of the anastomosis and with a view to postoperative cholangiography (Fig. 2).

In five of the 18 patients the attempt at resection had to be abandoned because of the spread of neoplasm to the portal vein bifurcation. Palliative operations were therefore performed, namely: biliary–jejunal anastomosis in two patients; a Dogliotti-type hepatogastric anastomosis[8] in one patient; and a transtumoral procedure in two patients.

In two of the 18 patients the radical tumor resection anticipated could not even be attempted because laparotomy revealed metastatic lesions in the liver in one (a man 79 years old in poor general condition) and extension of new growth to the liver parenchyma and the gall bladder in the other. Treatment was by simple external biliary drainage and palliative biliary–jejunal anastomosis respectively.

The 17 palliative decompressions (Table 2) performed in the 29 patients (nine before and eight after 1974) included 13 biliary–jejunal anastomoses, one hepatogastric anastomosis, one external biliary drainage, and two transtumoral intubations. Six palliative decompressions were performed electively and 11 were done of necessity, either because of extension of neoplastic growth, or because resection had proved to be impracticle, or for both of these reasons.

Operative Techniques

Our first step after opening the abdomen is to perform transhepatic cholangiography, unless retrograde cholangiography or transhepatic cholangiography using an Okuda needle has been done preoperatively with a satisfactory result. Preoperative transparietohepatic cholangiography is often incomplete, opacifying the right biliary passages only, in which case complementary peroperative cholangiography is required. The cholangiogram obtained should visualize the entire intrahepatic biliary tree, and demonstrate the degree of dilatation of the intrahepatic bile ducts and the site and

---

* Designation of hepatic segments in this paper follows Couinaud's nomenclature.[4,7,20]

TABLE 1. *Data of 11 Patients Who Had Resection of Carcinoma of the Hepatic Hilus*

Patient No.	Age/ Sex	Type of Resection	Site of Biliary Anastomosis	Postoperative Survival (Days)
1	63/m	MHDJ + right extended lobectomy	Left HD	12
2	72/f	MHDJ	Reconstructed MHDJ	514
3	62/f	MHDJ + resection of segment IV	Left and right HD	720
4	41/f	MHDJ + left lobectomy	Paramedian and right lateral HD	749
5	77/f	MHDJ* + resection of right branch of hepatic artery	Upper part of MHDJ	Alive** 1180
6	71/m	MHDJ*	Upper part of MHDJ	17
7	54/f	MHDJ + right extended lobectomy	Left HD	233
8	57/m	MHDJ + left lobectomy	Paramedian and right lateral HD	Alive** 452
9	64/f	MHDJ + left lobectomy	Right HD	Alive** 429
10	58/m	MHDJ	Reconstructed MHDJ	Alive** 249
11	67/m	MHDJ	Reconstructed MHDJ	Alive** 175

HD = hepatic duct. MHDJ = main hepatic duct junction. *In patients 5 and 6 the upper part of the MHDJ was preserved.

**On 18 August 1978.

intrahepatic extension of the tumor. Ideally, it should determine which of the three tumor types defined by Bismuth and Corlette[4] is present (Fig. 3).

These roentgenologic studies guide the surgeon in his choice of bypass procedure, in deciding whether the other lobe should be associated in the bypass and, if resection is to be done, in deciding whether hepatectomy will be needed. Our experience, however, like that of Longmire and associates,[15] has been that the operative procedure is determined more by the extent of invasion of the vessels or of liver parenchyma than by the roentgenologic findings.

If we elect to construct an intrahepatic biliary bypass to the bile duct of segment III at the beginning, with no attempt at resection, we use the technique described by Soupault and Couinaud.[20] The left margin of the ligamentum teres is dissected, giving access to the umbilical venous recess and to the portal triad of segment III, where the bile duct lies above and behind the portal inflow trunk. A side-to-side biliary anastomosis on a Roux-en-Y 80 cm jejunal loop is made with fine, nonabsorbable Polydeck 5-0 sutures. The anastomosis is to the junction of the duct of segment III with the left hepatic duct, but maximally to the latter as its more resistant walls and wider diameter allow of a wide anastomosis, around 2 cm, rarely calling for support by a transanastomotic drain. The anastomosis may be facilitated by opening the anterosuperior part of the fissure for ligamentum teres, and dissection of this fissure may itself be facilitated by dividing the band of liver parenchyma that joins the lower surfaces of segments III and IV. If peroperative cholangiography shows absence of communication between the left and right sides of the liver, a right intrahepatic bypass procedure should be associated.

When our initial aim is tumor resection, we use the operative technique outlined below, with the general objective of removing the neoplasm and re-establishing biliary continuity.

The tumor is dissected from the common duct to the intrahepatic bile ducts. On completion of the dissection, the stripped portal vein and hepatic artery should be the only structures visible in the hepatic hilus. The common bile duct should not be divided at the upper border of the duodenum until it has been ascertained that there are no local contraindications to resection (invasion of the portal vein bifurcation is the most common). A useful aid in the dissection is to separate the main lobar fissure along a cleavage plane passing through the gall bladder bed and projecting posteriorly toward the vena cava, but this step should also await confirmation of the absence of local contraindications to resection. Neglect of this precaution could result in the develop-

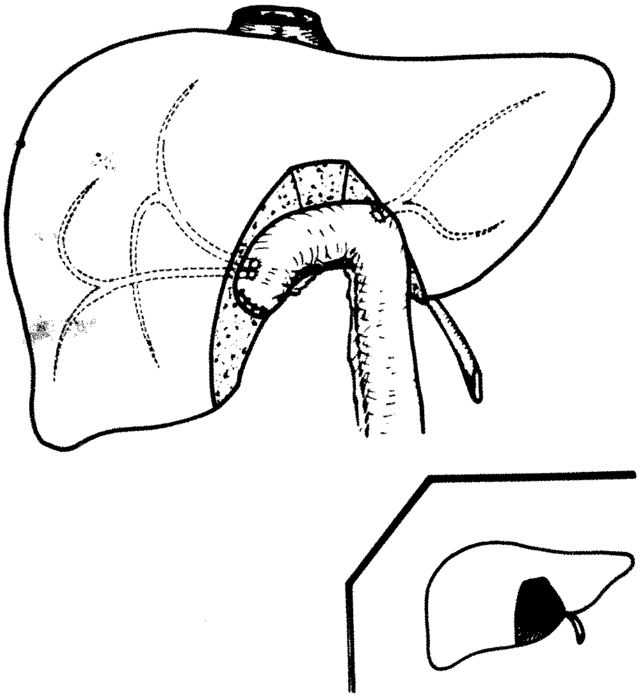


FIG. 1. Diagram of operation performed on patient 3. After resection of segment IV (Couinaud's terminology[1,7,20]), performed in order to obtain adequate exposure of the hilus of the liver, an *en bloc* excision of the entire major hepatic duct junction, the gall bladder, the cystic duct, and the common bile duct, was performed, and followed by anastomosis to a Roux-en-Y jejunal loop. The right hepatic ducts, divided proximal to a secondary junction, were inserted into the jejunal loop in a "double-barrelled" manner; the left hepatic duct was inserted into the loop direct.

ment of a biliary fistula at the cut hepatic surface if the surgeon had to settle for a simple palliative anastomosis. Exposure and resection of the tumor are sometimes facilitated if, after opening the fissure for ligamentum teres between the quadrate lobe and the left anterolateral segment (segment III), one mobilizes or resects the quadrate lobe (segment IV).

Periductal extension of tumor growth to the left or right branch of the hepatic artery or of the portal vein necessitates, in our experience, a left, right, or extended right hepatectomy.

After resection of the diseased portion of the hepatic duct, the biliary tract is reconstructed by means of an 80 cm Roux-en-Y excluded jejunal loop. This biliary–enteric anastomosis is constructed end-to-side, either on the main hepatic duct junction preserved or reconstituted, or on the left, right, or segmental hepatic duct.

Results

Survival

Survival times are summarized in Tables 1 and 2. Of the 11 patients who had tumor resection, two (patients 1 and 6) died in the immediate postoperative period (first 30 days after operation). Patient 1 (aged 63) had severe hypoalbuminemia and hypergammaglobulinemia; he died on the twelfth postoperative day in hepatic coma associated with gross and irreversible ascites. Patient 6 (aged 71), who also had hypoalbuminemia and hypergammaglobulinemia, died on the seventeenth postoperative day from a biliary fistula and gastrointestinal hemorrhage.

The mean survival time for the nine patients (mean age 61.3 ± 10.6 years) who survived the immediate postoperative period after tumor resection is 521 days (with a range of 175–1180 days). Three patients (2, 4, and 7) died at home 514, 749, and 233 days after resection. A fourth patient (3) was readmitted to the hospital for jaundice that appeared 705 days after resection. Laparotomy revealed a recurrent neoplastic growth narrowing the lumen of the intrahepatic Roux-en-Y loop, and a side-to-side jejunojejunal anastomosis was constructed. She did well the first two postoperative weeks, and then died from cholangitis. The remaining five patients (5, 8, 9, 10, and 11) were alive 1180, 452, 429, 249, and 175 days after resection.

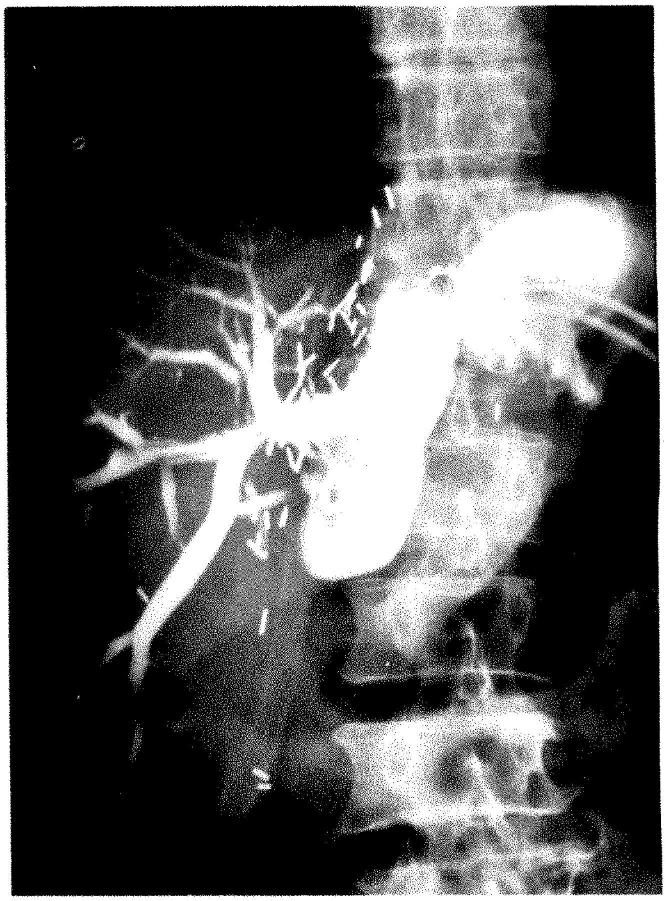


FIG. 2. Postoperative cholangiogram of patient 8. The biliary tract was reconstructed by inserting the paramedian and right lateral hepatic ducts into a Roux-en-Y jejunal loop. A transanastomotic tutor drain was used to strengthen the anastomosis.

TABLE 2. *Survival Times of 29 Patients After Operations for Carcinoma of the Hepatic Hilus*

Surgical Procedure	Period	Number of Patients: Total	Number of Patients: Postoperative Deaths*	Number of Patients: Survivors	Mean Postoperative Survival and Range (Days)
Palliative decompression	1968–73†	9‡	3	6	164 (51–344)
	1974–78	8§	3	5	208 (102–397)
Resection	1974–78	11	2	9	521 (175–1180)
Exploratory laparotomy	1968–73	1	1		
	Total	29	9	20	

* Up to thirtieth postoperative day.

† During this period no resections were attempted.

‡ Five elective, four of necessity. Biliary-jejunal anastomosis in all nine.

§ One elective, seven because resection failed or could not be attempted. Biliary-jejunal anastomosis in four, hepatogastric anastomosis in one, transtumoral drainage in two, and external biliary drainage in one.

In three patients subphrenic abscesses developed in the dead space resulting from left or right hepatectomy; all were treated successfully. In one patient jaundice persisted after extended right hepatectomy, although cholangiography showed complete patency of the biliary–jejunal anastomosis. Cholangitis did not develop in any of the 11 patients who had tumor resection, except secondarily in patient 3.

Of the 17 patients who underwent palliative decompression operations, whether conducted electively or after unsuccessful attempts at resection, between 1968 and 1978, six died during the immediate postoperative period. The mean age of these six patients at the time of operation was 72.7 ± 6.7 years, as contrasted with the mean age, 57.4 ± 8.9 years, of the 11 patients who survived the postoperative period ($p < 0.01$). The mean postoperative survival time for the 11 patients who survived palliative decompression was 184 days (range 47 to 397 days): 178 days for the nine patients who had had palliative biliary–jejunal anastomosis and 213 days (142 and 284) for the two patients who had had transtumoral intubation.

Morbid Anatomy

All the resected tumors were adenocarcinomas of the proximal bile ducts. Neoplastic growth extended to the cystic duct in four patients, to the periductal tissues in four patients, to the liver parenchyma in two patients, and to the gall bladder in one patient. In three cases there were metastatic deposits in lymph nodes in the hilus of the liver. Neoplastic invasion of the divided end of the common bile duct was found in four patients, a fact which confirms the usefulness of peroperative biopsy.

Discussion

The policy change we adopted in 1974, namely, to attempt surgical resection of tumors of the hepatic hilus in preference to the routine palliative biliary decompression practiced during the previous six years, has been justified in the event. Of the 18 patients for whom resection was planned, it was actually performed in 11, giving a resectability rate of 61%.

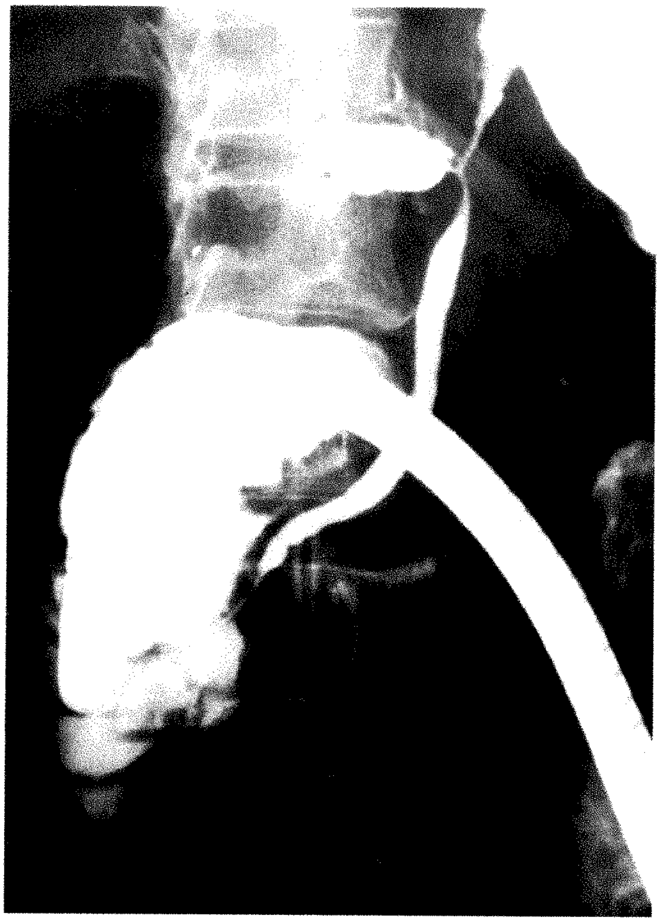


FIG. 3. Preoperative retrograde cholangiogram of patient 4. Both the main hepatic duct junction and a secondary junction are occluded by new growth (type III tumor of Bismuth and Corlette[4]). This patient had resection of the main hepatic duct junction, left lobectomy, and anastomosis of the paramedian and right lateral hepatic ducts to a Roux-en-Y jejunal loop. She survived the operation for 749 days.

Palliative biliary-jejunal anastomosis should not be undertaken routinely, without prior assessment of the resectability of the obstructing tumor. For predicting resectability, preoperative arteriography has found favor with some surgeons,[1,9,13] but not greatly with us, because it does not show whether the new growth has affected the blood vessel walls. The chief cause of tumor unresectability in our experience has been extension of neoplastic tissue to the portal vein bifurcation, which lies immediately posterior to the main hepatic duct junction.

The mortality associated with surgical resection of these tumors*[2,9,13] depends largely on whether hepatic resection is performed in addition to tumor resection. The operative risk is related to impaired liver function, which is increased by hepatectomy[16] and is manifested chiefly by hypoalbuminemia and hypergammaglobulinemia. These were present in our two patients (1 and 6) who died during the postoperative period, although in fact only one of them (patient 1) had had lobectomy. The remaining five patients who had segmentectomy or lobectomy survived for periods ranging from 233 to 749 days. A low postoperative mortality rate in resections confined to the common bile duct, the hepatic duct, and the main intrahepatic bile ducts has been reported.[13] That tumor resection without hepatic resection may be undertaken with a good prospect of success even in elderly subjects is suggested by our patient 5, a woman who was 77 years old at the time of the operation and was still alive 1180 days later.

The long-term survival times reported after resection vary.[1,2,9,13,15,19] One cause of difficulty in assessing survival times is that the results obtained in tumors of the proximal bile ducts have not always been reported separately from those pertaining to tumors of the biliary tract as a whole. The exact sites of the tumors in three patients who lived for five years or more after resection of biliary tract carcinoma[19] are not clear, since the investigator included the supraduodenal common bile duct in his definition of proximal bile ducts. These cases apart, there are well documented survival times ranging from five[13] to 38 months.[2] Our mean survival time was 521 days, and five patients were alive at intervals ranging from 175 to 1180 days after resection. These results are an encouragement to continued attempts at curative resection.

Cholangitis supervening during the postoperative course may indicate tumor recurrence. In such cases hepatic rose bengal or Tc-99m Hida scintiscanning may be a valuable diagnostic aid. It is often the only investigation that will demonstrate intrahepatic biliary retention. Proved recurrence may in some cases be treated by radiotherapy.[13]

Persistent jaundice after hepatectomy in one of our patients, in the presence of a patent biliary-jejunal anastomosis, could perhaps be related to the significant amount of hepatic tissue removed.[16]

The results reported with palliative biliary-jejunal anastomosis compare unfavorably with those obtained with tumor resection. Analysis of intrahepatic biliary-jejunal anastomoses reported here and elsewhere†[2,3,6,7,9–12,14,17,18] reveals a mean postoperative death rate of 40% and a mean survival time of seven months. Of the many postoperative complications reported (biliary fistula, cholangitis, and sepsis and septicemia[4,6,15,18]) cholangitis is the most frequent and the most lethal. The satisfactory results described by some surgeons[4,18,19] can, in our experience, be obtained only in patients under 65, above which age the immediate postoperative mortality rate is prohibitive. In our series, the mean age in the patients who survived the postoperative phase was significantly lower than in those who did not. The results reported with transtumoral intubation are similar to the best results reported with biliary-jejunal anastomosis. Of these two procedures, some surgeons prefer transtumoral intubation.[21]

Tumors of the hepatic hilus are not all of bile duct origin,[3] although all our resected tumors were in fact adenocarcinomas of the proximal bile ducts. Blumgart's (unpublished) series of seven cases included one carcinoma of the gall bladder extending to the hilus, one primary hepatocellular carcinoma, one mixed hepatoma-cholangiocarcinoma, and four cholangiocarcinomas. Of these, three (the hepatocellular carcinoma, the hepatoma-cholangiocarcinoma, and one cholangiocarcinoma) were successfully resected. As Bismuth and Corlette[4] have remarked, the mechanical problem confronting the surgeon is the same, whatever the origin of the tumor.

References

1. Alexandre, J.-H., Petite, J.-P., Germain, M., et al.: Chirurgie d'Exérese dans les Cancers des Canaux Biliaires Intrahépatiques. Chirurgie, 99:356, 1973.
2. Andersson, A., Bergdahl, L. and van der Linden, W.: Malignant Tumors of the Extrahepatic Bile Ducts. Surgery, 81:198, 1977.
3. Bertrand, L., Prioton, J.-B. and Ciurana, A.-J.: Le Cancer du Confluent Biliaire Supérieur, dit "du Hile". Presse Méd., 78: 1213, 1970.
4. Bismuth, H. and Corlette, M. B.: Intrahepatic Cholangioenteric Anastomosis in Carcinoma of the Hilus of the Liver. Surg. Gynecol. Obstet., 140: 170, 1975.
5. Brown, G.: Surgical Removal of Tumors of the Hepatic Ducts. Postgrad. Med., 16:79, 1954.

---

* Blumgart, L. H. Personal Communication.

† Launois, B. and Campion, J.-P. Unpublished Work.

6. Chapuis, Y. and Delaitre, B.: Thirty-two Observations de Dérivations Intra-hépatiques pour Blocage Hilaire. Ann. Chir., 29:301, 1975.
7. Couinaud, C.: Cholangiojéjunostomies Intra-hépatiques Gauches. A Propos de 18 Observations Personnelles. Arch. Fr. Mal. App. Dig., 56:295, 1967.
8. Dogliotti, A. M. and Fogliati, E.: Resection of the Liver with Intrahepatoductogastrostomy or Intrahepatoductojejunostomy for Biliary Obstruction. J. Int. Coll. Surg., 26:267, 1956.
9. Fortner, J. G., Kallum, B. O. and Kim, D. K.: Surgical Management of Carcinoma of the Junction of the Main Hepatic Ducts. Ann. Surg., 184:68, 1976.
10. Guillemin, G., Dubois, J., Braillon, G., et al.: Valeur et Indications des Dérivations Cholangio-jéjunales Intra-hépatiques dans la Chirurgie de l'Ictere par Rétention. A Propos de Neuf Observations. Mém. Acad. Chir., 91:484, 1965.
11. Hepp, J., Moreaux, J. and Lechaux, J. P.: Les Anastomoses Bilio-digestives Intrahépatiques dans les Cancers des Voies Biliaires. Résultats de 62 Observations. Nouv. Presse Méd., 2:1829, 1973.
12. Hivet, M. and Poilleux, J.: Les Cancers de la Voie Biliaire Principale Pédiculaire. Problèmes Chirurgicaux à Propos de 18 Cas. Ann. Chir., 29:265, 1975.
13. Iawasaki, Y., Ohto, M., Todoroki, T., et al.: Treatment of Carcinoma of the Biliary System. Surg. Gynecol. Obstet., 144:219, 1977.
14. Le Neel, J. C., Leborgne, J., Mousseau, P. A., et al.: Cancers de la Voie Biliaire Principale. Méd. Chir. Dig., 2:295, 1973.
15. Longmire, W. P., Jr., McArthur, M. S., Bastounis, E. A., et al.: Carcinoma of the Extrahepatic Biliary Tract. Ann. Surg., 178:333, 1973.
16. Pack, G. T. and Molander, D. W.: Metabolism Before and After Hepatic Lobectomy for Cancer. Arch. Surg., 80:685, 1960.
17. Perissat, J., Diard, F., Gouffrant, J.-M., et al.: Cancers de la Voie Biliaire Principale. Intérêt de la Cholangiographie Transpariéto-hépatique Pré-opératoire. A Propos de 31 Cas. Ann. Chir., 29:281, 1975.
18. Ragins, H., Diamond, A. and Meng, C.-H.: Intrahepatic Cholangiojejunostomy in the Management of Malignant Biliary Obstruction. Surg. Gynecol. Obstet., 136:27, 1973.
19. Ross, A. P., Braasch, J. W. and Warren, K. W.: Carcinoma of the Proximal Bile Ducts. Surg. Gynecol. Obstet., 136:923, 1973.
20. Soupault, R. and Couinaud, C.: Sur un Procédé Nouveau de Dérivation Biliaire Intra-hépatique. Les Cholangiojéjunostomies Gauches sans Sacrifice Hépatique. Presse Méd., 65: 1157, 1957.
21. Terblanche, J.: Is Carcinoma of the Main Hepatic Duct Junction an Indication for Liver Transplantation or Palliative Surgery? A Plea for the U tube Palliative Procedure. Surgery, 79:127, 1976.
22. Wanebo, H. J. and Grimes, O. F.: Cancer of the Bile Duct: The Occult Malignancy. Am. J. Surg., 130:262, 1975.

Risk Reduction in Gastric Operations for Obesity

EDWARD E. MASON, M.D., KENNETH J. PRINTEN, M.D., PATRICIA BARRON, JEFFREY W. LEWIS, M.D.,
G. P. KEALEY, M.D., THOMAS J. BLOMMERS, PH.D.

From the Department of Surgery,
University of Iowa College of Medicine,
Iowa City, Iowa

Although nearly devoid of late complications, gastric operations for obesity have resulted in 4.7% early postoperative perforations. For patients over 39 years of age who perforated, the first 11 patients died and the last 9 survived. Perforations are equally common in upper stomach, anastomosis, and lower stomach. They have become more frequent with the 50 ml upper stomach volume and 12 mm stoma that are required to assure optimum weight control. Perforation is as common with gastroplasty as with gastric bypass. If it occurs, it is normally within the first ten postoperative days. Acute dilatation and rupture of the stomach can happen if all the nasogastric tube holes are in the jejunum after gastric bypass. Erosion of the stomach by the hard end of the nasogastric tube has occurred when the tube was positioned in the upper stomach. This paper is dedicated to the prevention of death by early recognition and aggressive management of perforation and by prevention of perforations through careful attention to the details of these operations and early postoperative care.

IN GENERAL, SURGICAL PROCEDURES are justified on the basis of risk and benefit. By limiting the use of operations for obesity to patients more than twice their estimated ideal weight, the benefit to life style, health and the probable increased life span can be high enough to warrant the limited morbidity and mortality imposed by an operative procedure. As the risk of the operation is decreased, its use can be extended to more patients whose morbid obesity predisposes them to diabetes, hypertension, degenerative arthritis, heart failure and other complications. The success or failure of treatment of each obese patient with a new procedure has implications for all future patients. It is, therefore, in the interest not only of current patients but of all future and potential patients that risk be studied in detail and reduced as rapidly as possible.

Gastric operations for obesity were introduced with gastric bypass[5-7,10] in 1966. Specifications for success of these operations consist of a 50 ml upper pouch volume together with a 12 mm stoma. Weight reduction results from a decrease in food intake similar to a weight reduction diet. The construction of a diminutive stomach introduces a significant risk of gastric perforation (40 in 863 operations, 4.6%). A surprising observation is that perforation occurs only in the early postoperative period, usually due to errors in operative technique or in early postoperative management. Gastric perforation is amenable to early recognition, effective management and prevention. This paper will explain how the mortality rate has been lowered and how the causes of perforation can be corrected.

Recognition of Perforation and Peritonitis

Early recognition and reoperation after perforation is the key to recovery with minimal morbidity. We have discharged patients as soon as ten days after early reoperation, while other patients have been hospitalized as long as 161 days primarily because of delay in reoperation. The mean length of stay for reoperated patients has been 37 days. The combination of physician inexperience and patients older than 39 years of age produced a mortality rate of 100% prior to October 1, 1975 (Table 1). Since October 1, 1975, in spite of a two-fold increase in the incidence of perforation, survival has been 100%. This has been due to early recognition, prompt reoperation (Fig. 1) and the type of management described below. The effect of early recognition and better management is less apparent for younger patients but is no less important.

Early recognition of perforation is accomplished primarily by a surgeon's attitude towards complications. While an operation is in progress it is proper for the surgeon to feel that nothing could possibly go wrong with such a well performed procedure. As soon as the last suture is placed, however, the attitude of the surgeon should change to one of looking for a complication and wanting to be the first to recognize it. Such an attitude should be reinforced by the informed consent of patients who know that reoperation could be required.

Reprint requests: Edward E. Mason, M.D., Department of Surgery, University Hospitals, Iowa City, Iowa 52242.

Submitted for publication: March 1, 1979.

0003-4932/79/0800/0158 $00.90 © J. B. Lippincott Company

TABLE 1. *Survival Rates for Patients Who Have Had Perforations**

	Experience Prior to Oct 1, 1975			Experience After Oct 1, 1975		
Age	Operations	Perforations	Survivors	Operations	Perforations	Survivors
39+	211	11 (5.2%)	0 (0%)	116	9 (7.8%)	9 (100%)
38–	329	8 (2.4%)	6 (75%)	201	12 (6.0%)	10 (83%)
Total	540	19 (3.5%)	6 (32%)	317	21 (6.8%)	19 (90%)

* The patients are separated according to their age and the authors' experience in management.

Pain is a prominent symptom with perforation (Table 2) in contrast to uncomplicated recovery. Obese patients with uncomplicated gastric bypass move themselves out of bed and walk without undue discomfort, even on the evening of their operation. Incisional pain is usually minimal when the patient is lying quietly. Palpation of the abdomen during the early postoperative period is important. This is true even for uncomplicated patients because it prepares the surgeon to recognize signs of peritonitis when a leak is present. Normally patients have minimal tenderness. Shoulder pain, back pain, diffuse abdominal pain and pelvic pain are unusual and require investigation. Obese patients usually prefer a semirecumbent position because it facilitates breathing. As a result, if perforation occurs, the pelvic peritoneum is bathed in irritating digestive juices. According to nursing staff recollections, pelvic symptoms such as frequency and incontinence of urine or vaginal pain have been more common than previously recognized. Failure to record these symptoms in the past was due to the fact that we were not aware of their implications.

Patients with peritonitis appear anxious, ashen and sweaty. They express fear. They are short of breath due to increased requirements for gas exchange and because deep breathing is painful. They may be up and about seeking relief by change in position. Compared to the uncomplicated patient who often looks and acts as though no operation had been performed, these patients appear ill. If a morbidly obese patient becomes difficult to manage and a complainer postoperatively, it is not a manifestation of some special characteristic of the morbidly obese but rather a possible indication of a serious complication.

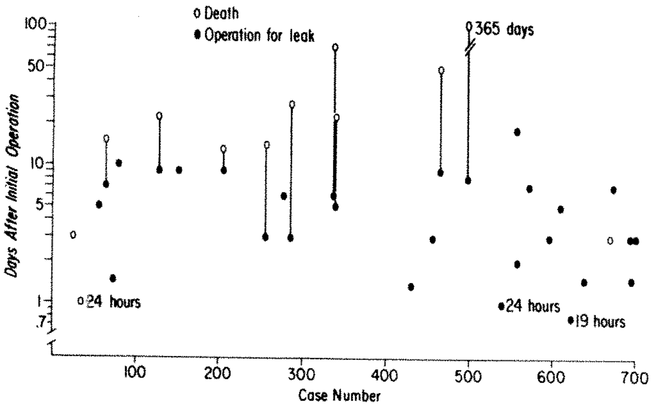


FIG. 1. Day of reoperation and death if it occurred, are plotted against case sequence number. With more timely reoperations, deaths have become less common.

The single most helpful sign in diagnosing peritonitis is abrupt tachycardia. During the first postoperative day the average pulse plus one standard deviation for patients without perforation is 120 beats per minute. Only four patients with perforation failed to have a pulse higher than 120 per minute. Twenty patients had a pulse rate above 150 per minute and 14, above 160 per minute.

Perforations are about equally common in the upper stomach, at the anastomosis and in the lower stomach (Fig. 2). The pyloric ring prevents contrast media from reaching the bypassed segment. It is not surprising, therefore, that 17 of 30 upper gastrointestinal radiographic studies were negative. A water soluble agent was used because of the problems arising when barium enters the peritoneal cavity. If a Hypaque® study is negative, the stomach contents should be aspirated and a small amount of thin barium instilled. In at least three patients the Hypaque was injected into the nasogastric tube. Consequently, a perforation in the upper stomach was bypassed and missed because the tube holes were beyond the stoma. The position of the tube both caused the perforation and prevented its detection. A negative roentgenogram should not be considered as conclusive evidence of an intact gastrointestinal tract. Eleven studies with Hypaque showed

TABLE 2. *Type and Frequency of Recorded Complaints in 36 Patients with Perforation*

Complaint	Frequency
Abdominal pain	25
Shoulder pain	15
Back pain	9
Shortness of breath	18
Sensation of fullness (urgency to void)	4
Anxiety	5

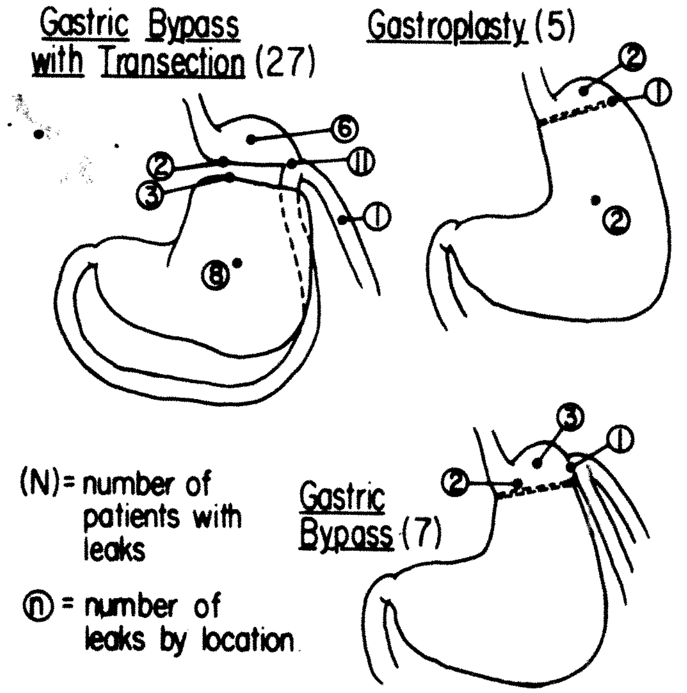

Gastric Bypass with Transection (27)
Gastroplasty (5)
⑥
⑪
②
③
①
⑧
②
①
②
(N)= number of patients with leaks
ⓝ = number of leaks by location
Gastric Bypass (7)
③
①
②

FIG. 2. Shows the location of perforations in 39 patients who were explored after the three different types of operations. Number of patients are shown in parentheses and number of perforations in each location is given in the circles. In the case of Gastric Bypass (7 patients), the precise location of perforation could not be determined in one patient.

neither the contrast material nor air in the peritoneal space even though all of these patients had operatively proven perforation. Exploration must often be undertaken on the basis of clinical signs and symptoms if morbidity and mortality are to be reduced.

Management

When the presence of a perforation has been established or is suspected, effective nasogastric suction must be assured. In some patients tachycardia and pain may be due to gastric distention. If decompression can be established soon enough by appropriate placement of the nasogastric tube or even by operative placement of a gastrostomy in the lower stomach, perforation can actually be prevented.

Extracellular fluid volume must be restored to guarantee adequate circulation and urinary output. This can be completed in the operating room. Several patients have been oliguric or even anuric when the operation commenced but were diuresing actively by the end of the operative procedure. Intravenous Clindamycin and Gentamicin are begun preoperatively. Operatively, the abdominal wound must be opened completely and the sites of perforation identified and closed. Only 12 patients had single sites of perforation. Feeding and suction enterostomies and a suction gastrostomy are popular in patients with peritonitis and the prospects of a prolonged postoperative course. In these patients, who often have hidden veins, a feeding enterostomy is of great value because there may be a prolonged period when the upper gastrointestinal tract must be at rest, even though the majority of the small bowel is functioning normally. Witzel enterostomies should be performed. This is necessary because these patients are difficult to mobilize postoperatively and, if the tube is accidently pulled out while the patient is trying to move, any hole torn in the wall of the stomach or intestine will thus be safely in the depths of the Witzel tunnel rather than open to the peritoneal cavity.

If the site of the perforation or perforations can be found and securely closed and if the peritoneal cavity can be properly debrided, drains are not necessary. Sometimes the site of the perforation cannot be found or is inaccessible. In such a case it may be elected to place drains in the area. Drains of all kinds have been used. Sometimes they are not needed and often they do not function well. Probably the best drain is a composite made from a Penrose drain with multiple holes cut in its wall and two Robinson catheters inside of the Penrose. One large catheter with multiple holes is used for suction and a smaller catheter for air or for irrigation with sterile saline.

In addition to early reoperation with drainge and closure of perforations, the most important addition to the treatment of peritonitis is radical debridement, recommended by Hudspeth.[4] The sooner the reoperation, the less fibrin will be found and the more likely that irrigation with sterile saline will suffice to clean the peritoneal cavity. If fibrin has formed, it should be removed as completely as possible from all peritoneal surfaces throughout the abdomen to reestablish normal function for the peritoneal surface in its extraction of bacteria. Finally irrigation with sterile saline is continued until the fluid is clear.

If experience with these problems is limited, there is a temptation to consider abandoning the operation. Conversion of a gastroenterostomy to a gastrogastrostomy may be a more satisfactory approach. There have been several attempts to close off the anastomotic sites and rely on gastrostomies to drain the two segments. This is the least satisfactory solution and assures the patient of at least one more and usually multiple operations with consequent increased risk of death.

Temperature probes should be placed in the patient's rectum and/or esophagus before the reoperation is begun. If the temperature is in the range of 40° the irrigating fluid can be cooled to help reduce the patient's fever. Radical debridement may increase operating time to three or more hours but the time is well spent and justified. There are occasional patients whose perforation is recognized late but who have been able to localize an abscess to the subphrenic space without generalized soiling of the peritoneal cavity. For these patients drainage of the local abscess may be sufficient. For most patients, however, the approach described above is preferable and, if there is any question about which way to direct the treatment, the radical debridement with the entire peritoneal cavity exposed is preferable.

Postoperative Care

Severe peritonitis even in the thin patient can cause death by what Burke, Pontoppidon and Welch[2] have called high output respiratory failure. These patients often require postoperative ventilatory support. The endotracheal tube is left in place and a volume regulated ventilator is used. Septic obese patients develop respiratory failure because they cannot tolerate the increased respiratory demands of the hypermetabolic septic state. Therefore, they must be ventilated to relieve them of the work of respiration and cooled artificially to lower their metabolic needs. Cooling may be difficult because of the thick layer of fat. It may be necessary to curarize these patients and place them between two cooling blankets to achieve proper thermal control.

Whereas expansion of the extracellular fluid is usually needed before and during the operation, there may be fluid overload postoperatively. Close monitoring of pulmonary artery and wedge pressures through a Swan-Ganz® catheter, systemic pressure measurement, urinary output and blood gases help to direct proper management. Pulmonary perfusion pressure is influenced by obesity, positive pressure breathing and sepsis. The difference between pulmonary artery diastolic and pulmonary wedge pressure is of help in evaluating the progress of sepsis.[11] Serial cardiac outputs help to determine the need for blood plasma and additional fluids. Cooling is used to counteract hyperpyrexia but not to produce hypothermia. The earlier re-explorations are undertaken the simpler the postoperative care. The improvement in survivorship is evident in Table 1 and Figure 1. In fact, the only recent death from perforation involved a patient in whom the surgeons failed to recognize the classical signs and symptoms and did not re-explore the patient.

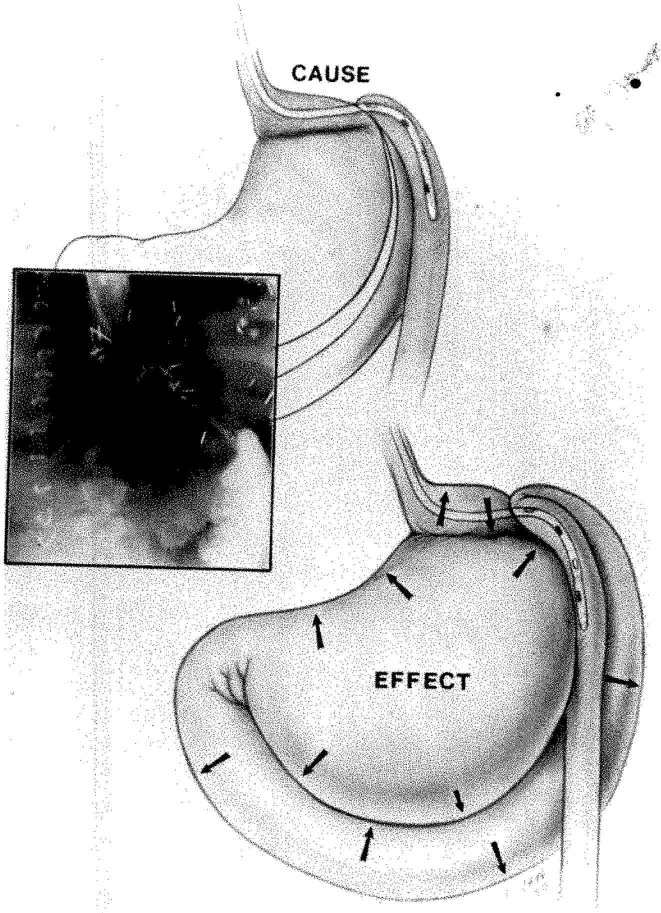


FIG. 3. Shows how placement of the nasogastric tube through the gastroenterostomy stoma may result in failure of the tube to prevent distention of the entire stomach. This is because all of the openings in the tube are in the efferent limb of the jejunal loop.

Prevention of Perforation

It would be easier to solve the problems of perforation if there were only one cause. Unfortunately, there seem to be multiple causes but most are related to the position and function of the nasogastric tube. We are at the stage in the use of this operation at which some of the complications are probably the result of trying too hard to prevent all of the problems of the past. The situation is analagous to the early days of Billroth II gastrectomy when duodenal stump leaks led to the use of more sutures and this in turn led to more leaks. In some respects it may be the same problem except that we have reason to believe that now the perforations are the result of excessive gastric distention rather than poor closure of the bypassed segment. There is evidence in some patients that the nasogastric tube failed to decompress the stomach because the openings in the tube were beyond the gastroenterostomy stoma and located in the efferent limb of the jejunal loop. As a result, the upper stomach, the afferent jejunal limb, the duodenum and the distal stomach became markedly distended (Fig. 3). The obvious response to observing such a complication is to

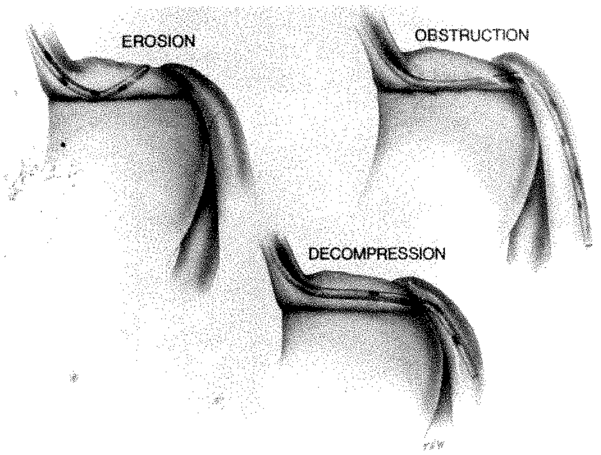


FIG. 4. Shows too shallow, too deep and correct placement of the nasogastric tube in gastric bypass. Both erosion and obstruction have caused perforation.

position the nasogastric tube so that all of the openings will be in the lower esophagus and upper stomach.

Having arrived at such a simple conclusion the senior author performed a gastroplasty by stapling the stomach and leaving a 50 ml volume upper segment and a 12 mm diameter passage along the greater curvature. The nasogastric tube was positioned entirely in the upper stomach. Upon completion of the operation the end of the tube was observed to be pressing on the wall of the greater curvature of the upper stomach and was, therefore, withdrawn a short distance before the abdomen was closed. The nasogastric tube seemed to be working well because 50 ml of swallowed water would promptly return. On the second day slightly bloody drainage appeared and the volume of nasogastric drainage increased. These observations brought to memory patients in whom removal of the tube, in the presence of increasing nasogastric drainage before passage of flatus, had been followed by perforation of an obstructed upper stomach. For this reason the nasogastric tube was left in place. The pH of the gastric secretions dropped to two by color indicator paper and, according to the suggestion of Gomez,[3] cimetidine was administered. Finally on the fourth day there was passage of flatus and the tube was removed. However, by this time the patient's temperature elevated to 39° and the pulse rate increased to 120 per minute. Hypaque swallow was obtained and demonstrated extravasation. In the interim the patient had developed left shoulder and abdominal pain and frequent urination in small amounts, all signs of peritoneal irritation.

Reoperation showed a hole in the anterior wall of the stomach just above the stoma where the end of the nasogastric tube had been seen at the conclusion of the initial operation. The hole had the appearance of pressure necrosis. It was the exact size of the plastic nasogastric tube that, incidently, has a very firm tip. The mucosa was healed to the serosa and was not protruding. There was almost no reaction in the surrounding stomach wall and the opening did not have the radiating tears that are characteristic of rupture from distention. The patient commented on the second day following gastroplasty that there was strong tugging on the nasogastric tube. Apparently peristalsis pulled the tube down and this had re-established pressure of the tip against the stomach wall and had eroded through. We have seen similar perforations, although not yet in an obese patient, in which a gastrostomy tube has been inserted too far. Malecot catheters have now replaced stiff catheters for use in gastrostomies. The plastic nasogastric tubes are not rigid enough to be passed down the esophagus during an operative procedure without at times doubling up. However, the end of the tube is too rigid to rest in one position against the wall of the stomach without perforating that wall.

The small size and boot shape of the upper stomach in both gastric bypass and gastroplasty contributes to the problem of perforation (Fig. 4). The nasogastric tube must make two nearly right angle turns, one at the cardia and the other at the gastroenterostomy, if the tube is positioned through the stoma. Placement of the tube a few centimeters through the stoma positions the end of the tube in a relatively safe area. If the tube is placed entirely in the upper stomach the combination of the bend at the cardia and the pressure of the stapled stomach on the side of the tube immobilizes the tube and holds its end against the anterior wall of the stomach near the greater curvature and just above the stoma. This is the site of most of the perforations that have occurred in gastroplasty in our experience. This is also the area where perforations have occurred in the experience of Gomez.

With the nasogastric tube posing a risk from being positioned too deeply, causing distention because all holes are beyond the stoma or too shallow and making erosion more likely, perhaps the best solution would be to not use a nasogastric tube at all and to rely on a gastrostomy placed in the lower stomach. Provided that the tube functioned properly and the stoma were patent, this would decompress both the upper and lower stomach. If both a nasogastric tube and gastrostomy were used the nasogastric tube could be removed early on the morning following operation. The gastrostomy tube should be a soft nosed Malecot catheter, positioned so that the opening is just within the gastric wall and will not cause pressure on the opposite wall. It should be positioned far enough below the area where the stomach is stapled to assure that there will not be pressure on the staple line. Reliance on the gastrostomy without a nasogastric tube or with early removal of the nasogastric tube requires assured patency of the small stoma draining the upper stomach. Lewis, in our group, recommends intraoperative injection of air into the upper stomach as a means of determining patency. Sometimes the construction of the stoma can leave an obstructive flap valve.

With regard to the prevention of perforation, what can be recommended for gastric bypass should also be applied to gastroplasty (Table 3) because the factors contributing to the problem (small volume, boot shape and small outlet of the upper stomach) are the same. In both procedures there is a need for removal of swallowed air and secretions before excessive distention is created. Because there is limited room for the tube, which must be positioned properly to function well, there is a reluctance on the part of the surgeon to change the position of the tube after the abdomen is closed. The narrow tortuous passage through the cardia, upper stomach and stoma contributes to the fixation of the lower end of the tube and the development of what appear to be "pistol shot" erosions through the wall of the stomach.

Another risk with the small upper stomach is occasioned by early ventilation with a mask after the patient is extubated. Every surgeon is familiar with the occasional patient who had a large amount of air in the entire gastrointestinal tract after a difficult induction of anesthesia. It is possible to force a great deal of air into the gastrointestinal tract and if a small upper stomach has been created it would be easy to burst this segment. The endotracheal tube should be kept in place and used for suctioning and ventilation until the patient is sufficiently alert to manage secretions and to get along without ventilatory assistance. Ventilation of the patient with a mask is definitely contraindicated in these patients.

Gomez has interpreted the "pistol shot" perforations in the upper stomach as perforated stress ulcers. To prevent this he has established a routine of administering cimetidine to all his patients for the first four or five days after their operation. Other surgeons have been analyzing the nasogastric juice and administering cimetidine only if the pH drops below two. Stress ulcers certainly could cause perforation. Why they should be located most often in the toe of the boot shaped upper stomach, however, is uncertain. At the present time we can not deny that at least some of the perforations are due to stress ulcerations. Therefore, we are treating patients with cimetidine if there seems to be an excessive secretion of very acid gastric juice. Nevertheless, it seems that the most likely cause of perforations in this area is due to erosion from the tube.

There have been other causes of stomach perforations after these operations. In those patients who have had a Roux-en-Y enterostomy, care must be taken to prevent narrowing at the site of the enteroenterostomy from use of a stapled closure of the opening in which the GIA® stapler has been inserted. The afferent limb coming from the duodenum to the enteroenterostomy is placed behind the long limb so that it will make a gentle curve. We have not seen obstruction from kinking in any of our obese patients, but other patients who have had a Roux type of gastroenterostomy have developed a kink of the afferent limb just proximal to the anastomosis when it was placed on the patient's right side. This is caused by peristalsis that carries the afferent limb to the left thus creating the kink. An afferent limb of a loop gastroenterostomy which is too long can create the same problem since peristalsis will force the afferent loop to the patient's left and kink the jejunum at the anastomosis. When using a retrocolic gastroenterostomy, the mesocolon opening can be too small and may slide down. If this occurs, the two limbs of the jejunum pull together causing obstruction. If there are adhesions or potential sites for internal herniation, the early postoperative ileus may evolve into a mechanical bowel obstruction. At this time the excluded stomach may distend to the point of perforation if bowel obstruction develops. Later, after the patient has recovered and the stomach has regained its tone, obstruction will not cause distention of the stomach to the extent of perforation. The stomach under these circumstances seems to pump the contents back into the small bowel causing additional intermittent pain thereby encouraging the patient to seek medical attention in time for re-exploration before perforation.

TABLE 3. *Risk of Perforation and Risk of Death from Perforation According to the Type of Operation Performed*

	Gastric Bypass (GB)	Gastroplasty (GP)	Revision of GB	Conversion GP → GB	Total
Procedures	620	82	130*	25	857
Perforations	25 (4.0%)	5 (6.1%)	9 (6.9%)	1 (4.2%)	40 (4.7%)
Deaths	11 (1.8%)	1 (1.2%)	2 (1.5%)	0 (0.0%)	14 (1.6%)

* One hundred fifteen patients had 130 revisions.

Some surgeons feel that leaks, particularly from an anastomosis, are prima fascie evidence of poor blood supply.[8] We have always taken great care to preserve lesser curvature blood vessels. We do not dissect the area rather, we simply pass a Robinson catheter close to the lesser curvature and feed the toe of the stapler into the back end of the catheter so that it may be guided into place. We use a lesser curvature point, 5 cm below the cardia, for stapling across the stomach as described by Alder and Terry.[1] This gives added

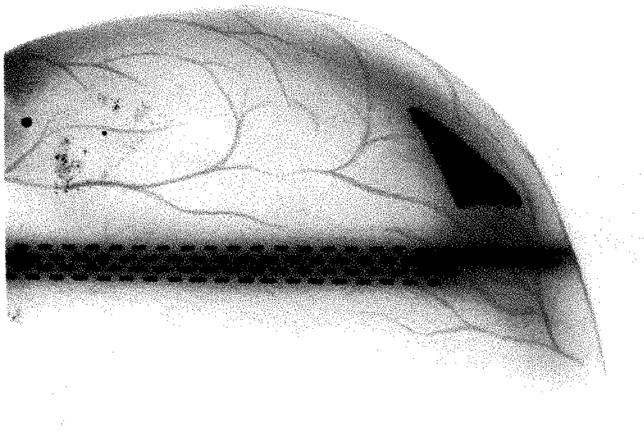


FIG. 5. Shows staple line at greater curvature. Second set of staples is left incomplete to enhance blood supply.

assurance that an adequate blood supply will come into the stomach above the area of stapling.

Blood supply can be compromised by the congestion of staples and/or sutures. Many surgeons have had occasional staple failure in patients following stapling without stomach transection. In fact, two of our patients have not only had formation of a passage between the upper and lower stomach, because of staple disruption, but a simultaneous leak outside of the stomach. In response to this problem some surgeons are using a second set of staples close to the first set. If an anastomosis is made on the greater curvature, the staples or sutures of this anastomosis will decrease small vessel blood flow to the tissue between the anastomosis and the transverse staple line. For this reason the second set of staples across the stomach should be incomplete at the greater curvature so that some blood will flow through the stomach wall and through the staples subjacent to the gastroenterostomy (Fig. 5). Blood flow through two rows of staples has been demonstrated by bleeding if the tissue is cut and by Wood's light inspection after fluorescein injection as shown by Myers.[9] If too much space is left between two parallel applications of staples (four rows of staples) then necrosis may occur between the inner two rows. Should this develop, it may progress into the staple line with resultant perforation. If two applications of staples are used they should be close enough together so that the two inner rows are approximately as far apart as the outer rows.

If the stomach is transected, as was the routine when this operation was first introduced, the corner of the upper stomach segment at the greater curvature should be cut off and this opening used for an end-to-side anastomosis rather than making a separate anastomosis above the closed end of the stomach. This will provide a better blood supply to the anastomotic area. It is possible to create an anastomosis above a two row application of staples across the intact stomach and maintain adequate blood supply between the two stapled or sutured areas. However, this is not always the case if the stomach has been transected rather than stapled (Fig. 6).

There is need for a small stoma in order to prevent future overeating. There is, no doubt, even a need for some measure to keep the stoma from stretching. We have had patients lose weight only to report after a year or two that they could suddenly eat more and had begun to regain weight. It is likely that sutures have pulled through and scar tissue has stretched allowing the gastroenterostomy or gastroplasty stoma to become considerably larger. There have been efforts to prevent stretching of the stoma by placing a running nonabsorbable 3-0 Prolene® seromuscular suture around the stoma in gastroplasty. In one patient a chromic catgut suture was placed through the stomach wall near the end of the line of staples and near the passage that had been left along the greater curvature. This catgut suture was then tied down on the outside surface of the stomach in order to calibrate the stoma around an inlying 28 F Hurst dilator. The 3-0 Prolene seromuscular suture was then placed circumferentially, overlying the groove which had been created. After removal of the Hurst dilator the stapled end of the stomach was held in such a position that it was invaginating the wall of the stomach into the stoma and blocking the passageway. This contributed to a perforation of the stomach above the stoma. This type of complication can be prevented by placing the sutures in such a way that the end of the line of staples is not pulled into the lumen. In addition, however, it is

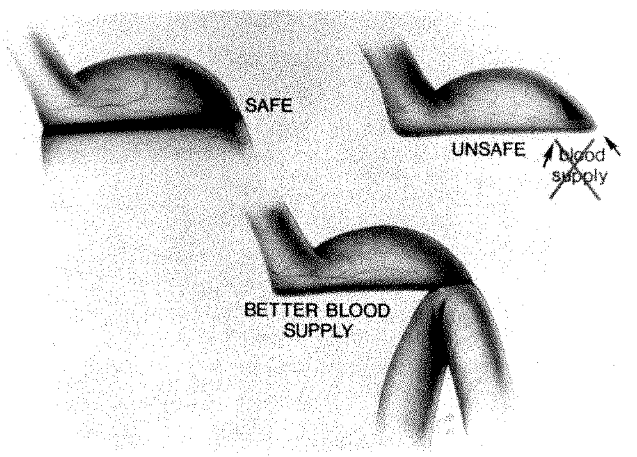


FIG. 6. Illustrates why the gastroenterostomy should be placed at the end of the upper segment when the stomach has been transected instead of stapled in continuity.

advisable to have the anesthesiologist place saline in the upper stomach to determine patency by observing the saline passing through the stoma before the abdominal wound is closed. Gastroplasty is still under investigation but it is being used in varying modifications by increasing numbers of surgeons. The basic principles are quite similar to those of gastric bypass. A small nonstretching stoma combined with the small volume of the upper segment are essential; and therein lies the hazard of obstruction and perforation.

Patient Education

Surgeons are perpetual optimists. They believe that they can create a situation within the abdomen which is markedly different from anything the patient has had to contend with before and that the patient will learn to cope with a minimal amount of instruction. Actually, these patients are like tigers in regard to eating and drinking. It is illogical to think that a wild animal can be contained in an orange crate. These patients need a great deal of instruction and early supervision. We have had patients rupture their stomachs on the day of operation by sneaking a drink from the sink or from their roommate's water pitcher. Patients should be given a set of plastic medicine glasses on their first visit and told to start practicing the style of eating and drinking that will be required after their operation. If this advise is not acceptable to a prospective patient then he or she is simply not a candidate for this type of operation. Gastric bypass and gastroplasty are behavior modification procedures with a vengance and patients should be so informed. Perforation is a vanishing risk after the first ten days because patients become aware of distension and desist. Awareness of these hazards on the part of surgeons is required to prevent early perforation.

Addendum

When autopsy is not permitted, early postoperative deaths are often attributed to pulmonary embolism. The cause of death is more likely to have been peritonitis according to our experience, vide supra. With this in mind, review of the records of all unproved deaths following gastric bypass and gastroplasty is strongly recommended and will perhaps be the best educational exercise that can be provided for those who have had such patients. Hopefully there are few such undiagnosed deaths. Nevertheless, this is something that must not be overlooked. Perforation with resultant peritonitis is much more amenable to treatment than pulmonary embolism, if diagnosed.

References

1. Alder, R. L. and Terry, B. E.: Measurement and Standardization of the Gastric Pouch in Gastric Bypass. Surg. Gynecol. Obstet., 144:762, 1977.
2. Burke, J. F., Pontoppidon, H. and Welch, C. C.: High Output Respiratory Failure: an Important Cause of Death Ascribed to Peritonitis or Ileus. Ann. Surg., 158:581, 1963.
3. Gomez, C.: Am. J. Clin. Nutr., in press.
4. Hudspeth, A. S.: Radical Surgical Debridement in the Treatment of Advanced Generalized Bacterial Peritonitis. Arch. Surg., 110:1233, 1975.
5. Mason, E. E. and Ito, C.: Gastric Bypass in Obesity. *Cl. N. Amer.*, 47:1345, 1967.
6. Mason, E. E., Printen, K. J., Hartford, C. E. and Boyd, W. C.: Optimizing Results of Gastric Bypass. Ann. Surg., 182:405, 1975.
7. Mason, E. E., Printen, K. J., Blommers, T. J. and Scott, D. H.: Gastric Bypass for Obesity after ten years Experience. Int. J. Obesity, 2:197, 1978.
8. Maini, B. S., Blackburn, G. L. and McDermott, W. V., Jr.: Technical Considerations in a Gastric Bypass Operation for Morbid Obesity. Surg. Gynecol. Obstet., 145:907, 1977.
9. Myers, B. Personal communication.
10. Printen, K. J. and Mason, E. E.: Gastric Surgery for Relief of Morbid Obesity. Arch. Surg., 106:428, 1973.
11. Sibbald, W. J., Paterson, N. A. M., Holliday, R. L., et al.: Pulmonary Hypertension in Sepsis. Chest, 73:583, 5 May 1978.

Stapled Cystogastrostomy

A Method of Treatment for Pediatric Pancreatic Pseudocyst

F. TAGHIZADEH, M.D., R. J. BOWER, M.D., W. B. KIESEWETTER, M.D.

An uncommon complication of pancreatic inflammatory disease or pancreatic trauma in children is the development of a pseudocyst. The English literature records less than 100 cases in children and emphasizes that surgical intervention is the indicated form of treatment. The authors have had experience with nine pediatric patients suffering from pseudocysts in a seven year period. All except one were successfully treated by internal drainage; the other spontaneously resolved. Four had cystogastrostomy using a stapler. This method is discussed as far as indications, technique, advantages and complications.

From the Surgical Clinic of the Children's Hospital of Pittsburgh and the Department of Surgery of the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

An uncommon complication of pancreatic inflammatory disease or pancreatic trauma in children is the development of pseudocyst. The literature emphasizes that surgical intervention is indicated in its management. Many methods have been suggested, but because all children are affected metabolically and physically by the cyst, the simplest and least hazardous procedure should be performed. Cystogastrostomy fits these requirements best and has been used by a number of surgeons.[11] Employment of a stapler is a new method for making the anastomosis more simply and safely. The advantages of stapled anastomosis have been well documented in intestinal resection. We believe that the same advantages are obtained in cystogastrostomy.

We will briefly review our experience with pancreatic pseudocysts at the Children's Hospital of Pittsburgh during a seven year period. From this, we will comment more specifically on four patients whose cysts were handled by the stapled cystogastrostomy technique.

Clinical Material

Between 1970 and 1977, a total of nine patients were diagnosed as having a pseudocyst of the pancreas. Approximately 95 cases of this entity have been reported in the English speaking literature. Table 1 lists the clinical findings in the nine patients seen at our institution.

Blunt trauma plays a definite role in the pathogenesis of this lesion. While over 80% of pseudocysts in adults are a complication of alcoholic pancreatitis,[12] 59% of those in children are due to blunt abdominal trauma.[3] Other causative factors in childhood are pancreatitis, hyperlipidemia, biliary tract disease, steroid therapy, mumps and cytotoxic drugs. The cause in a number of patients remains unknown.

A pediatric pseudocyst usually causes abdominal pain, nausea, vomiting, fever, anorexia and weight loss. On physical examination the most common consistent findings are an abdominal mass and tenderness; a pancreatic pseudocyst usually presents as a retrogastric mass, occasionally extending to the mediastinum[4] or paracolic gutter. An elevated serum amylase and leukocytosis are the most common positive laboratory findings. Hyperglycemia, hyperbilirubinemia, elevated alkaline phosphatase levels, hypovolemia and hypoalbuminemia have also been reported when pseudocyst is present.[7] A plain abdominal x-ray of the abdomen usually is not helpful, but an upper gastrointestinal series has demonstrated a mass in 66–88% of the cases.[3,6] Examination by ultrasound and arteriography have been increasingly helpful in making the diagnosis.[2]

Case Reports

Case 1.(F.N.) This 4-year-old white girl was admitted in December 1974 with a three week history of vague abdominal pain, low grade temperature, nausea and vomiting. The parents reported that the child lost eight pounds during this period. They also gave a questionable history of their daughter falling from her bed 36 hours prior to admission. On physical examination, the child appeared chroni-

---

Reprint requests: William B. Kiesewetter, M.D., Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania 15213.

Submitted for publication: February 6, 1979.

0003-4932/79/0800/0166 $00.70 © J. B. Lippincott Company

TABLE 1. *Clinical Data*

Name and Year of Admission	Age, Sex	Short History	Trauma History	Pan-creatitis History	Serum Amylase	X-ray, US Findings	Procedure	Post-operative Complications	Post-operative Condition
A.V. 1970	7 yrs, male	Admitted with abdominal pain, tenderness L.U.Q. and palpable mass L.U.Q. for 2 days	No	No	—	IVP revealed cystic mass left side	Exp. laparotomy, excision cyst of pancreas and splenectomy	None	Doing well
W.P. 1974	13 yrs, male	3 months history of trauma in abdomen Referred with enlarging mass in epigastrium L.U.Q.	Yes	Yes	793	Sonogram revealed cystic mass	Exp. laparotomy, cystojejunostomy	None	Doing well
J.H. 1974	10 yrs, male	One day history of blunt abdominal trauma, pain and vomiting	Yes	Yes, traumatic	1308 900	—	Exp. laparotomy, injury of tail of pancreas; sump drainage	Yes, pseudocyst of pancreas	Doing well ↓ appetite
Second adm., 10 days after 1st admission					1600	Cystic mass behind stomach	Cystogastrostomy		Doing well
J.V. 1974	6 yrs, male	History 5 days fall from bike with vomiting and upper abdominal pain and anorexia. PE: palpable mass mid epigastrium	Yes	No	1600	UGI revealed cystic mass behind stomach, ultrasound also revealed cystic mass	Cystogastrostomy *Stapler*	None	Doing well
F.N. 1974	4 yrs, female	3 weeks history abdominal pain, nausea, vomiting, low grade fever, weight down. PE: vital signs stable, palpable mass mid epigastium; otherwise normal	Fell from bed	No	2610 239	UGI revealed mass behind stomach post duodenum right side	Cystogastrostomy *Stapler*	None	Doing well
C.C. 1975	15 yrs, female	History of bloody vomiting and abdominal pain for 9 months. PE: palpable mass epigastrium; otherwise normal	No	No	209 131	UGI and sonogram sonogram revealed cystic mass	Roux-en-y pancreatic cystojejunostomy	None	Doing well
K.J. 1976	3½ yrs, male	Trauma to abdomen. PE: there is tenderness in epigastrium and distention, B.S. normal, no palpable mass and multiple abrasions, bruises on the skin	Yes	No	248	UGI and ultrasound revealed 1–5 cm cystic mass	Observation Repeat sonography showed no cyst	—	Doing well
V.N. 1977	5 yrs, male	Suddenly developed epigastric pain, vomiting	No	No	430–399 486 2950	Ultrasound revealed cystic mass behind stomach	Cystogastrostomy *Stapler*	None	Doing well
M.C. 1977	4 yrs, female	Admitted for history of vomiting, abdominal pain. PE: palpable mass mid epigastrium	No	No	970 107 1500	UGI and ultrasound revealed cystic mass	Exp. laparotomy, cysto-gastrostomy *Stapler*	Cystogastrostomy opening spontaneously closed	
							Repeat cysto-gastrostomy *Stapler*		Doing well

cally ill and the upper abdomen was tender with a palpable mass in the midepigastrium. Her white blood cell count was 19,000 and her serum amylase 2,610. An arteriogram revealed an avascular mass in the pancreatic area. A GI series showed displacement of the stomach and duodenum. At celiotomy a large pseudocyst in the body of pancreas was drained by a cystogastrostomy stapled anastomosis. She recovered without complications and at follow-up, two years later, was doing well.

Case 2. (I.V.) This 6-year-old white boy was admitted to our institution in August 1975 complaining of upper abdominal pain, anorexia, vomiting and low grade fever. He had a history of trauma secondary to a fall from his bicycle five days before admission. On physical examination the upper abdomen was tender with a palpable mass in the epigastrium. The serum amylase was 3,000 and the W.B.C. 12,000. An upper GI series delineated a retrogastric mass with displacement of the stomach anteriorly. Sonography suggested a cystic mass 16 × 18 cm in diameter. The patient was observed for two weeks to allow for maturation of the cyst wall. At celiotomy a large pseudocyst of the body of the pancreas was treated by a stapled cystogastrostomy. He recovered without complication and has remained well.

Case 3. (V.N.) This 5-year-old white boy was admitted in August 1976 for severe abdominal pain, low fever, and vomiting. On physical examination, the patient was in acute distress with severe epigastric tenderness, rebound tenderness, a W.B.C. of 11,000 and a serum amylase of 2,000. Suspecting a pancreatic pseudocyst, we ordered a sonogram which revealed a cystic lesion 4 × 5 cm in diameter. A repeat sonogram three weeks later, when conservative management allowed him to quiet down, showed an increase in the size of the cyst. At surgery the pancreatic cyst was found and drained using a stapler to effect a cystogastrostomy. The patient had an uneventful recovery.

Case 4. (M.C.) This 4-year-old black girl was admitted in October 1977 with abdominal pain and vomiting. On physical examination there was tenderness and a palpable mass in the epigastric area. The serum amylase was 15,000 and the W.B.C. 10,000. Both the upper GI series and sonogram demonstrated a retrogastric cystic mass with displacement of the stomach. The patient was observed for two weeks while on hyperalimentation to allow synthesis of the stomach and cyst to occur. At celiotomy a typical pseudocyst was drained by cystogastrostomy using the stapler. In the postoperative period her serum amylase again became elevated to preoperative levels and the abdominal mass returned. Gastroscopy revealed closure of the cystogastrostomy stoma. She underwent reexploration and reconstruction of her cystogastrostomy by excising some of the stoma to provide an ample opening. After the second operation, she recovered without complication and has remained well.

Cystogastrostomy

Indications

Cystogastrostomy should be considered for all cysts which are located in the retrogastric region and adherent to the posterior wall of stomach with a mature synthesis. It generally takes four to six weeks for such adherence to occur after pancreatitis or trauma.

Advantages

Cystogastrostomy is the simplest procedure to adequately drain the cyst internally. Using this procedure the mortality, morbidity and recurrence are low. This is in contrast to the significant morbidity and mortality with cystojejunostomy or cystoduodenostomy.[10,11]

Technique

An upper midline incision of the abdomen is generally used. After exploration and evaluation as to whether cystogastrostomy is indicated and possible, an 8 cm transverse incision is made in the anterior wall of the stomach. The posterior wall of stomach is palpated to define the most prominent point of the cyst. The cyst is then aspirated to confirm the diagnosis and define the area where a cystogastrostomy can be constructed. Through a 2 cm incision on the posterior wall of the stomach parallel with mucosal folds, the stapler is inserted to staple–incise an opening about 6 cm long. The anterior wall of the stomach is then closed in a routine two-layer manner.

Complications

Two complications are said to occur in cystogastrostomy—postoperative gastrointestinal bleeding and reflux of food and hydrochloric acid into the cyst cavity. One complication we encountered, the opening between the stomach and cyst closed off requiring a second procedure, should be added to the list of complications.

Discussion

Once a pseudocyst of the pancreas has developed, the criteria for its treatment depend upon at least four factors: 1) The size of the pseudocyst; 2) the anatomic location of the cyst; 3) the maturity of the cyst wall; and 4) the presence or absence of infection. There is no doubt that small, asymptomatic cysts of the pancreas do arise following pancreatitis or trauma. Only since ultrasonography has been readily available has it become apparent that these can develop and then spontaneously resolve with no need for any surgical intervention.[14] All large cysts, as well as those which are increasing in size, must have some type of surgical treatment. The appropriate procedure depends upon the location of the cyst, the maturity of its wall and whether infection is present. Internal drainage is the procedure of choice and the site of the anastomosis depends upon the position of the cyst. A cystoduodenostomy is preferred when the cyst is located in the head of the pancreas. Generally speaking, a cystojejunostomy whether by direct anastomosis or by the interposing of a Roux-en-Y loop, can be used in any pseudocyst. It has the principal advantage of lessening the chance of gastric reflux into the cyst,[9] but the surgery is more extensive and difficult than a direct internal drainage anastomosis. Occasionally, a cyst can be totally excised if it is located in the tail of the pancreas and the cyst is small in extent; usually, a portion of the pancreas has to be sacrificed in doing this, but it is definitive when able to be performed. External drainage used to be the accepted method of therapy in most all cases and still has a place in certain special situations. If the patient is a poor risk and has been sick for a long time, one would prefer to simply drain the cyst to the outside. An immature and thin-walled cyst that is in danger of rupturing likewise may benefit by the simple expedient of external drainage. Infected cysts can be a life-threatening complication; the only course open under those circumstances is wide drainage to the outside.

Transgastric cystogastrostomy is easy, simple and effective. This is largely due to the fact that the cyst is directly behind and intimately adherent to the stomach so that an opening into the stomach can be readily accomplished. According to some researchers,[1,13] cystogastrostomy has the lowest incidence of operative mortality and recurrence when compared with other procedures. There are, however, some disadvantages to this method. Postoperative gastrointestinal bleeding has occurred in 3–50% of the patients.[8,11,15] In the face of bleeding, the mortality rate increases precipitously to a range of 50%.[6] This is usually due to the fact that the pancreatic enzymes present in the pseudocyst erode a major vessel. Occasionally, a similar finding may result from bleeding of the cyst wall itself. At least one author[8] has suggested that bleeding which occurs after cystogastrostomy may be the result of gastric reflux into the cyst cavity when the stoma between the two areas is overly large. Sometimes this is the result of the stoma having been oversewn after its creation. One has to often balance the desirability of oversewing the stomal edge to prevent anastomotic bleeding against the undesirability of making a larger communication whereby the gastric juice can enter the cyst cavity.[5,14]

We have not encountered bleeding in this very limited experience and have felt that the presence of the staples, themselves, has prevented the bleeding along the anastomotic edge and, at the same time, kept the stomal size to a minimum. By doing this the chance of gastric reflux into the cyst is lessened. One complication of this procedure is having the cystogastrostomy completely close (as happened in one of our cases). This was detected by the return of an abdominal mass and the resumption of an elevated serum amylase. A second procedure, again accomplished with the stapler, produced a somewhat larger opening between the stomach and the cyst.

The experience with the four patients cited has confirmed our feeling that cystogastrostomy with a stapler has a distinct place in the treatment of childhood pancreatic pseudocyst. The basic simplicity of the method makes it a good mode of therapy. The mechanical suturing assures a number of desirable features. The anastomosis will be completely immobile and stable. The stapling will prevent the minimal tearing which may occur with needle suturing. Finally, the staples themselves decrease the tissue trauma, inflammation and necrosis that goes with the standard suturing technique.

Acknowledgment

We would like to express appreciation to E. S. Wiener, M.D. for the inclusion of Case 1 (F.N.) in this study.

References

1. Becker, W. F., Pratt, H. S. and Ganji, H.: Pseudocysts of the Pancreas. Surg. Gynecol. Obstet., 127:744, 1968.
2. Rose, J. S., Becker, J. A., Staiano, S. J., et al.: Proceedings: B-Mode Sonographic Evaluation of Abdominal Masses in the Pediatric Patient. Am. J. Roentgenol. Radium Ther. Nucl. Med., 120:691, 1974.
3. Cooney, D. R., and Grosfeld, J. L.: Operative Management of Pancreatic Pseudocysts in Infant and Children: A Review of 75 Cases. Ann. Surg., 182:590, 1975.
4. Edlen, P.: Mediastinal Pseudocyst of the Pancreas: Case Report and Discussion. Gastroenterology, 17:96, 1951.
5. Folk, F. A. and Freeark, R. J.: Reoperations for Pancreatic Pseudocyst. Arch. Surg., 100:430, 1970.
6. Grace, R. R., and Jordan, P. H. Jr.: Unresolved Problems of Pancreatic Pseudocysts. Ann. Surg., 184:16, 1976.
7. Huang, T. T., Wolma, F. J., and Fish, J. C.: Metabolic and Hemodynamic Considerations in Patients with Pancreatic Pseudocyst. Surg. Gynecol. Obstet., 135:517, 1973.
8. Huston, E. L., Zeppa, R. and Warren, D.: Prevention of Postoperative Hemorrhage After Pancreatic Cystogastrostomy. Ann. Surg., 177:689, 1973.
9. Kilman, J. W., Kaiser, G. C., King, R. D., et al.: Pancreatic Pseudocysts in Infancy and Childhood. Surgery, 55:455, 1964.
10. Polk, H. C. Jr., Zeppa, R. and Warren, W. D.: Surgical Significance of Differential Between Acute and Chronic Pancreatic Collections. Ann. Surg., 169:444, 1969.
11. Schumer, W., McDonald, G. O., Nichols, R. L., et al.: Transgastric Cystogastrostomy. Surg. Gynecol. Obstet., 137:48, 1973.
12. Thomford, R. N. and Jesseph, J. E.: Pseudocyst of the Pancreas: A Review of Fifty Cases. Am. J. Surg., 118:86, 1969.
13. Tucker, P. C. and Webster, P. D.: Traumatic Pseudocysts of the Pancreas: A Report of Ten Cases. Arch. Intern. Med., 129:583, 1972.
14. Van Heerden, J. A. and ReMine, W. H.: Pseudocysts of the Pancreas: Review of 71 Cases. Arch. Surg., 110:500, 1975.
15. Warshaw, A. L., Inflammatory Masses Following Acute Pancreatitis. Surg. Clin. North Am., 54:621, 1974.

Evidence For a Pyloro–Cholecystic Reflex for Gallbladder Contraction

H. T. DEBAS, M.D., T. YAMAGISHI, M.D.*

From the Department of Surgery, University of British Columbia, Vancouver, B.C., Canada

We studied the effect of graded antral distension on gallbladder contraction both when gastrin release was promoted (alkaline distension) and when gastrin release was blocked (acid distension) in five dogs provided with innervated antral pouch, chronic bile fistula and gastric fistula. Graded distension of the antrum caused graded gallbladder contraction as evidenced by bilirubin output even when gastrin release was completely suppressed. This nongastrin mechanism of gallbladder contraction is abolished by parenteral atropine and by transthoracic truncal vagotomy. These observations provide evidence for a cholinergic, pyloro–cholecystic reflex for gallbladder contraction that is dependent on intact long vagal pathways. Similar reflex mechanisms have been shown to be initiated by antral distension and to cause pancreatic enzyme secretion (pyloro–pancreatic reflex) or acid secretion from the oxyntic gland area of the stomach (pyloro–oxyntic reflex). It would appear, therefore, that the antrum plays a central role in the integration of upper gastrointestinal function not only through the hormone gastrin but also through neural reflex mechanisms.

GASTRIN is known to have both choleretic and cholecystokinetic actions. This is not surprising since both gastrin and cholecystokinin (CCK) share the same five amino acids at the effector C-terminal end of their molecules. Until now any control the antrum might have on biliary function has been attributed solely to the hormone gastrin.

The recent discovery that antral distension stimulates pancreatic enzyme secretion not only through the release of gastrin but also through a neural pyloro–pancreatic reflex[3] led us to search for an analogous pylorocholecystic reflex. This study provides evidence for a cholinergic, vago–vagal, pyloro–cholecystic reflex for gallbladder contraction.

Methods

Animal Preparation

Each of five mongrel dogs, weighing between 22 and 28 kg, underwent three operations. In the first operation, a chronic bile fistula was prepared by placing a modified Herrera cannula[5] into a pouch created by separating a short segment of duodenum into which the common bile duct entered (Fig. 1). In each instance, the minor pancreatic duct was identified, ligated, and divided. The cannula allows bile drainage from the pouch into the duodenum when the limb to the exterior is capped. During studies, the cap is removed and a special obturator is threaded into the cannula to close off entry into the duodenum so that bile can flow to the outside for collection. In this system, gallbladder contraction is readily detected by a rapid outpouring of a large volume of concentrated bile, which is high in bilirubin content, and, unlike hepatic bile, contains low concentrations of bicarbonate. The bilirubin output can thus be used as an index of gallbladder contraction.

In the second operation, two weeks after the first, a vagally innervated pouch of the pyloric gland area or antral pouch (AP), and a gastric fistula were constructed in each dog. The AP was completely separated from the proximal stomach, care being taken to identify and preserve the anterior and posterior nerves of Laterjet as they coursed caudad to innervate the antrum. The transected pylorus was closed and a Gregory cannula was inserted into the body of the

---

* Current address: Department of Surgery, University of Tokyo, Tokyo, Japan.

A preliminary report appeared in abstract form and the data was presented at the Annual Meeting of the American Gastroenterology Association, Toronto, Canada, May 23–26, 1977.

Reprint requests: H. T. Debas, M. D., Department of Surgery, UBC, 700 West Tenth Avenue, Vancouver, B.C. V5Z 1L5, Canada.

Supported by grants from the National Institute of Arthritis, Metabolism and Digestive Diseases (1R01 AM18508-0) and the Medical Research Council of Canada (MA-5428). Dr. Yamagishi held a fellowship grant from the British Columbia Medical Services Foundation.

Submitted for publication: January 30, 1979.

0003-4932/79/0800/0170 $00.80 © J. B. Lippincott Company

pouch. Gastrointestinal continuity was restored by anastomosis between the body of the stomach and the proximal jejunum.

After completion of distension experiments which provided evidence for a pyloro-cholecystic reflex mechanism, we wanted to know whether this reflex was vago-vagal. In a third and final operation, the dogs underwent transthoracic truncal vagotomy in which a 2 cm portion of each vagus and any communicating branches were resected over the distal thoracic esophagus. Distention experiments were repeated after recovery from the operation.

Experimental Procedure

No experiments were conducted until at least three weeks had elapsed after each operative procedure. The animals were deprived of food but not of water for 18 hours before each test. Only two tests per week were performed on each animal, and always with at least two days between tests.

The responsiveness of each biliary fistula preparation was assessed by dose-response studies to exogenous cholecystokinin. The CCK used was 20% pure preparation purchased from the GIH Laboratories, Karolinska Institutet, Stockholm, Sweden. The doses employed were 1, 2 and 4 units/kg/hour, each dose being given as a continuous intravenous infusion over an hour, by which time the response to each dose was completed. Each dose was studied on a separate day.

In each experiment, prior to application of distension to the AP, two 10 minute basal samples of bile were collected. The AP was then filled with either 0.1M $NaHCO_3$ solution (pH 8.3) or 0.1M HCl solution (pH 1.1) from a barostat as described previously.[2] The effect of antral distension was studied with the barostat adjusted to the level of the AP (0 pressure), and with the barostat raised to 10, 20, 30 or 40 cm above the AP. The effect of only one pressure was studied per day. In some experiments, the animals were pretreated with atropine-sulfate (0.2 mg/kg subcutaneously), 15 minutes prior to filling the AP.

In all experiments, the gastric fistula was kept open. Bile was collected continuously by gravity and separated into 15 minute samples. Volume was measured to the nearest 0.1 ml. Bilirubin concentration was determined by measuring absorbance at 460nM, using a Beckman DB Spectrophotometer, of a sample of bile diluted 1:100 with distilled water, and using pure bilirubin solution (Fisher Scientific Co., Ltd., Vancouver, Canada) as standard. The bicarbonate concentration in bile was determined by adding 1.0 ml of 0.1M HCl to 0.5 ml samples, heating the mixture to the first evidence of boiling, and, when cooled, back-titrating the residual acid to pH 7.0 with 0.1M NaOH.

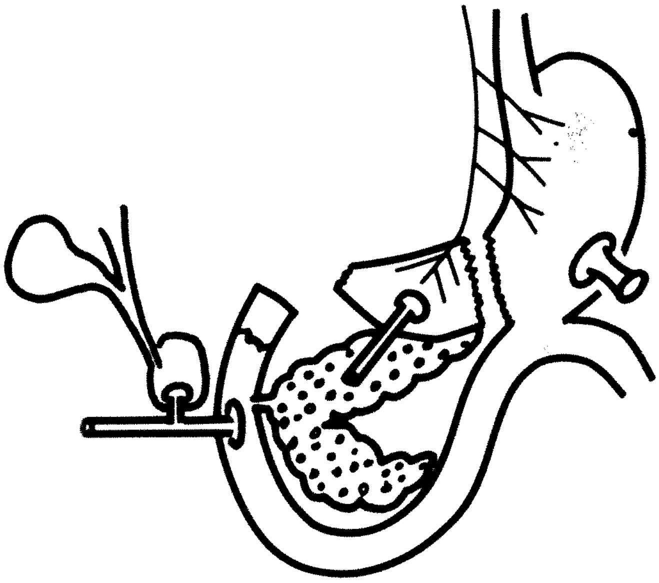


FIG. 1. Animal Preparation: Construction of chronic bile fistula using a modified Herrera technique, a separated but vagally-innervated antral pouch drained by a Gregory cannula and a chronic gastric fistula. Gastrointestinal continuity is restored by gastrojejunal anastomosis.

At the conclusion of each experiment, what bile was not used to perform determinations was returned into the duodenum so as to avoid chronic bile acid depletion in the animals.

Serum Gastrin Determination

In all distension experiments, two venous blood samples were obtained in the basal state when the AP was empty, then every 15 minutes after it was filled with solution from the barostat at various heights. Serum was obtained by centrifugation and was stored at −20° until assayed. Serum gastrin concentrations were determined using an antibody that cross-reacts with both the G-17 (little) and the G-34 (large) molecular forms of gastrin.

Statistical Analysis

The significance of the differences between mean basal bilirubin secretion and mean bilirubin response to antral distension was analysed using Student's t-test for unpaired values.

Results

Dose-Response Studies to Cholecystokinin

The bilirubin output from the bile fistula in response to the three doses of CCK is given in Figure 2. Each

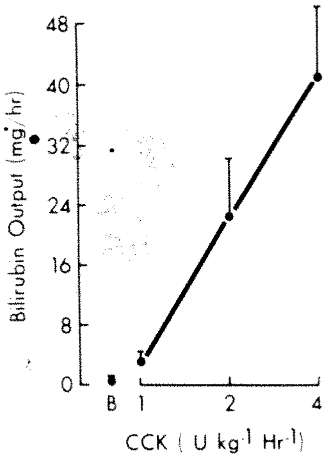


FIG. 2. Mean (±SE) bilirubin output from bile fistula in response to various doses of CCK. Each point represents the mean of two experiments in each of five dogs.

dose was tested on a separate day. The bilirubin output in response to the highest dose tested (4 U/kg/h) amounted to 41 mg in the first hour of infusion. The bile secreted in response to the various doses of CCK contained insignificant amounts of bicarbonate that increased little with increasing doses of CCK.

Effect of Antral Distension with 0.1M $NaHCO_3$

Graded antral distension with 0.1M $NaHCO_3$ caused graded bilirubin output from the bile fistula (Fig. 3, left panel). The increased response was both in volume of bile secreted and in bilirubin concentration. The response to antral distension at the highest pressure tested (40 cm fluid), amounted to 15% of the maximal bile output in response to 4 U/kg/h of exogenous CCK.

Graded antral distension also caused a graded rise in the concentration of immunoreactive gastrin in the circulation (Fig. 3, right panel). The mean basal gastrin was 69 ± 11. A significant release of gastrin ($p < 0.05$) occurred at distending pressures of 10, 30, and 40 where serum gastrin concentrations were 149 ± 32, 129 ± 21, and 204 ± 35 respectively.

Effect of Antral Distension with 0.1M HCl

Antral distension with 0.1M HCl also caused a strong gallbladder contraction as shown by the bilirubin output (Fig. 4, left panel). Only the higher three distending pressures caused a statistically significant bilirubin output ($p < 0.05$). Although the mean results do not achieve a level of statistical significance with the lower dose, we observed clear-cut gallbladder contractions on several occasions even with the smallest pressures. Observing these responses to low-level antral distension, the authors had the distinct impression that a gallbladder contraction under these conditions may be an "all-or-none" phenomenon.

Unlike alkaline antral distension, distension of the antral pouch with acid caused no increase in serum gastrin concentration over the basal value of 49 ± 8 (Fig. 4, right panel). Gallbladder response seen with acid distension cannot, therefore, be ascribed to the gastrin mechanism. The bicarbonate output in the bile secreted during both alkaline and acid distension is given in Table 1. There is a small but definite bicarbonate response with both types of distension.

Effect of Atropine and of Truncal Vagotomy

Pretreatment of the animals with atropine completely suppressed bilirubin output in response to antral dis-

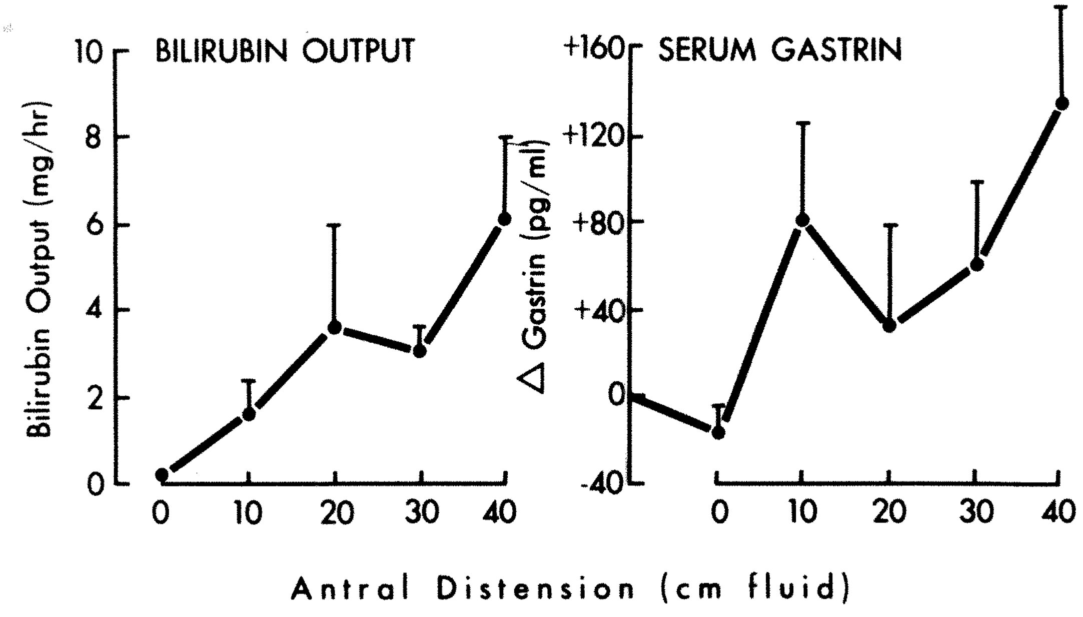


FIG. 3. Mean (±SE) bilirubin output from bile fistula (left panel) and increment in serum gastrin concentration (right panel) in response to graded antral distension with a solution of 0.1 M $NaHCO_3$. Each point represents the mean of two experiments in each of five dogs.

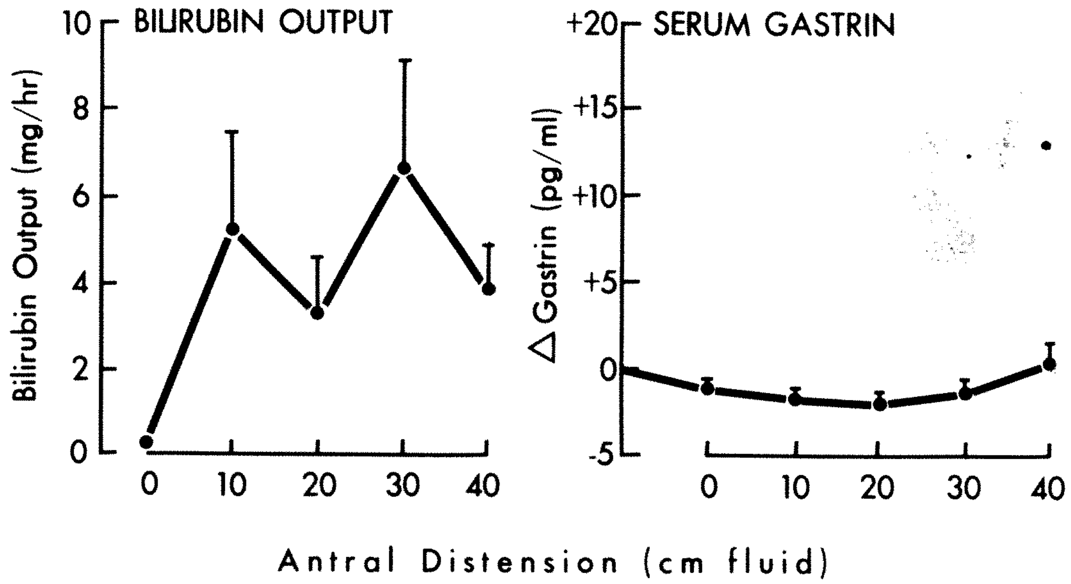


FIG. 4. Mean (±SE) bilirubin output from bile fistula (left panel) and change in serum gastrin concentration from basal (right panel) in response to graded antral distension with a solution of 0.1 M HCl. Each point represents the mean of two experiments in each of five dogs.

tension with either alkali or acid (Fig. 5). Similarly, following truncal vagotomy no gallbladder contraction occurred in response to antral distension with either alkali or acid. Gastrin response to antral distension with 0.1M $NaHCO_3$ after truncal vagotomy was 10% of the prevagotomy value. This small gastrin response was, presumably, not enough to cause a bile response.

Discussion

Graded antral distension with either alkali or acid resulted in a graded gallbladder contraction as evidenced by the rapid outpouring of bilirubin-rich, and bicarbonate-poor bile from the bile fistula. Alkaline antral distension was associated with a significant and graded rise in serum gastrin concentration. Since gastrin is able to contract the gallbladder,[4] the gallbladder contraction seen during alkaline antral distension may be, at least in part, gastrin-mediated. During distension of the antrum with acid, gastrin release was completely suppressed yet a gallbladder contraction still occurred in response to antral distension. This response could not be due to gastrin. Further, both atropine and truncal vagotomy completely abolished gallbladder contractions in response to acid antral distension. We conclude, therefore, that antral distension initiates a cholinergic, vago–vagal, pyloro–cholecystic reflex for gallbladder contraction.

In these studies, we found small amounts of bicarbonate secretion in bile. The secretion of bicarbonate in bile is largely from intrahepatic ductal cells which are sensitive to hormonal stimulation by secretin and to a lesser extent by CCK and gastrin.[1] In the gallbladder, there is a small but definite secretion of hydrogen ions, and the bicarbonate present in hepatic bile is no longer seen in gallbladder bile. We do not know the origin of this small amount of bicarbonate secretion seen in our study. The possible sources are the liver, the duodenal pouch used to collect the bile and possibly the pancreas via small ductules that may enter the duodenal pouch and which may not be grossly visible. The accessory duct that enters the duodenum close to the entry of the common duct had been divided in each dog. The design of the experiment does not permit a firm conclusion as to the source of the bicarbonate but we suspect it might have been the duodenal pouch into which the bile cannula was placed.

The maximum bilirubin response to antral distension with acid was 15% of the maximum response to exogenous CCK employed. During a meal a biphasic bili-

TABLE 1. *Bicarbonate Output in Bile (μEq/hr) Basally and After Antral Distension With Alkali or Acid*

		Antral Distension (cm Fluid)				
	Basal	0	10	20	30	40
Alkaline	9 ± 8	18 ± 12	329 ± 150	82 ± 50	86 ± 32	292 ± 100
Acid	11 ± 4	91 ± 53	177 ± 121	99 ± 22	99 ± 75	100 ± 85

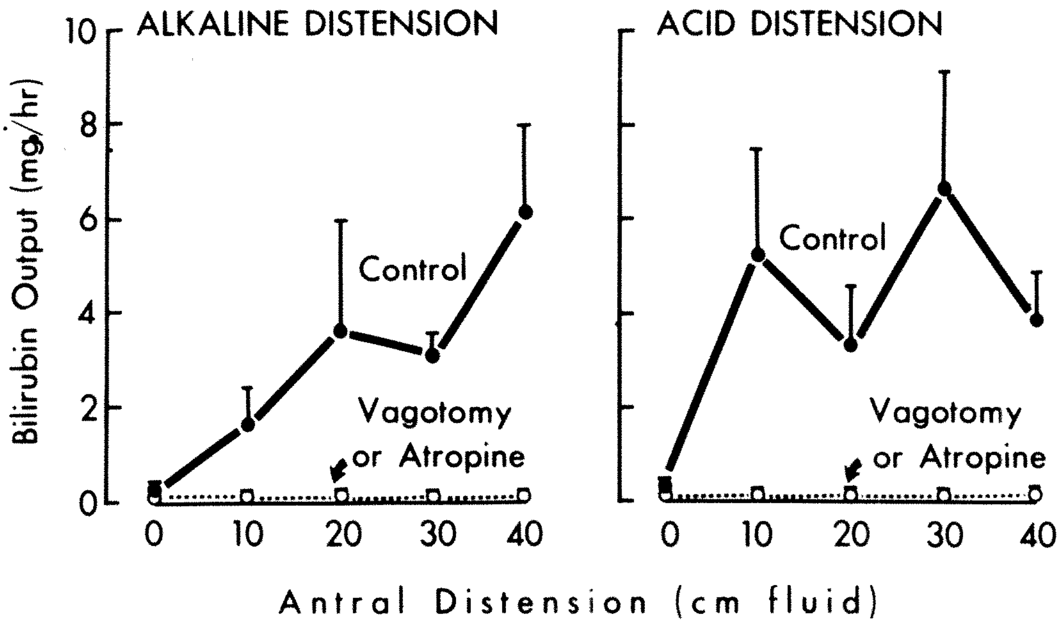


FIG. 5. Mean (±SE) bilirubin output from bile fistula in response to graded antral distension with 0.1 M $NaHCO_3$ (left panel), and 0.1 M HCl (right panel); with and without pretreatment of animals with parenteral atropine-sulfate; and before and after truncal vagotomy.

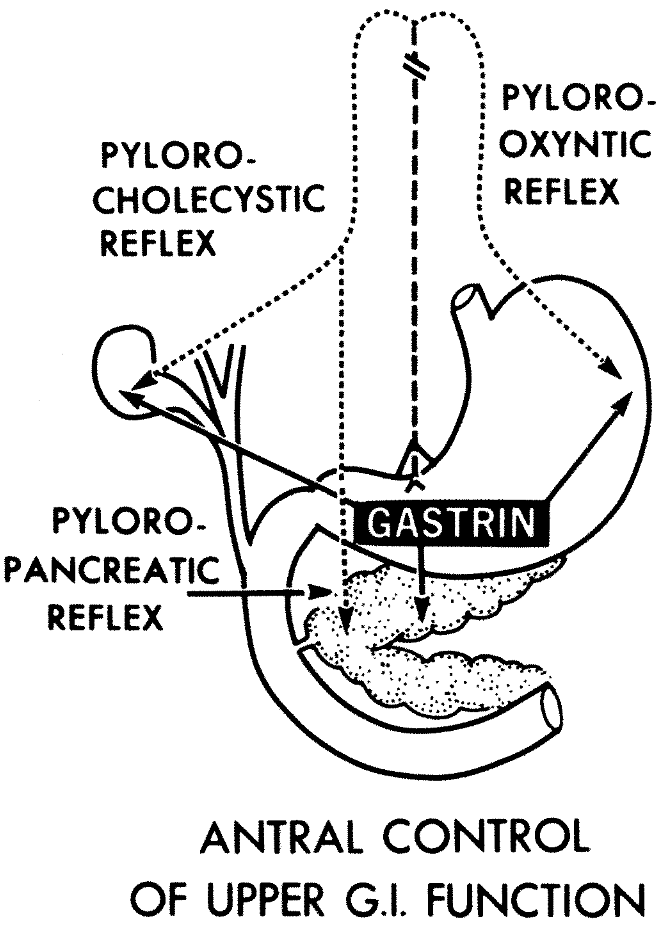

PYLORO-CHOLECYSTIC REFLEX
PYLORO-OXYNTIC REFLEX
GASTRIN
PYLORO-PANCREATIC REFLEX
ANTRAL CONTROL OF UPPER G.I. FUNCTION

FIG. 6. Antral control of upper GI function. Reproduced with permission from Debas, H. T. and Yamagishi, T.: Evidence for Pyloro-pancreatic Reflex for Pancreatic Exocrine Secretion. Am. J. Physiol., 234(5):E468, 1978.

rubin response is seen: The initial response, which occurs within the first 10 minutes of the meal, is smaller than the larger and a more prolonged response that starts 20–30 minutes after ingestion begins (personal observations). We hypothesize that the initial response is due to events in the stomach, *i.e.*, distension and gastrin release, and that this bile response is probably needed to emulsify the first portion of the chyme that enters the duodenum. Once a sufficient amount of chyme bathes the intestinal mucosa, an adequate CCK response occurs which is the predominant mechanism for gallbladder contraction. This CCK action is potentiated by small amounts of secretin released by acid chyme.[6] It would appear, therefore, that gallbladder contraction in response to a meal, has both a gastric and intestinal phase. The gastric phase is probably mediated, at least in part, by the pyloro–cholecystic reflex described here.

An analogous mechanism, the pyloro–pancreatic reflex, has recently been described. Antral distension also stimulates acid secretion from the proximal stomach not only by the gastrin mechanism but also through a cholinergic, pyloro–oxyntic reflex.[2] It would appear, therefore, that the antrum plays a central integrating role in the function of the proximal stomach, pancreas, and the gallbladder both through the hormone gastrin and neural reflex mechanisms (Fig. 6). These reflex mechanisms have been discovered using pouch dogs. Before they can be considered physiologically important they must be shown to operate in intact animals and in man. If indeed these reflexes operate in man, they are negated by such gastric procedures as truncal or selective vagotomy and antrectomy which may cause problems with the mixture of ingested food, pancreatic juice and bile by delaying the arrival of these digestive fluids to the duodenum early during the meal. This is yet another theoretical advantage for highly selective vagotomy over either truncal or selective vagotomy, since highly selective vagotomy would be expected to leave the pyloropancreatic and pyloro-cholecystic reflex mechanisms intact. This conclusion is supported by the work of LaVigne et al. who showed that the effects on pancreatic and biliary function of parietal cell vagotomy were minimal.[7]

Acknowledgments

We are grateful to Dr. M. I. Grossman for his helpful suggestions with the manuscript; to Mrs. Eileen Bonagura, Mr. K. L. Leung and Mr. Jan van den Broeck for expert technical assistance and to Mrs. Diane Steel for typing the manuscript.

References

1. Brooks, F. P.: The Secretion of Bile. Am. J. Dig. Dis., 14: 343, 1969.
2. Debas, H. T., Konturek, S. J., Walsh, J. H., et al.: Proof of a Pyloro-Oxyntic Reflex for Stimulation of Acid Secretion. Gastroenterology, 66:526, 1974.
3. Debas, H. T. and Yamagishi, T.: Evidence for a Pyloro-Pancreatic Reflex for Pancreatic Exocrine Secretion. Am. J. Physiol., 234(5):E468, 1978.
4. Grossman, M. I.: Gastrointestinal hormones: Spectrum of actions and structure-activity relations. *In* Chey, W. Y. and Brooks, F. P. (eds.) *Endocrinology of the Gut.* Thorofare, Charles B. Slack, Inc., 1975, pp. 65–75.
5. Herrera, F., Kemp, D. R., Tsukomoto, M., et al.: A New Cannula for the Study of Pancreatic Function. J. Appl. Physiol., 25:207, 1968.
6. Meyer, J. H., Spingola, L. F. and Grossman, M. I.: Endogenous Cholecystokinin Potentiates Exogenous Secretin on Pancreas of Dog. Am. J. Physiol., 221:742, 1971.
7. LaVigne, M. E., Wiley, Z. D., Martin, P., et al.: Gastric, Pancreatic and Biliary Secretion and Gastric Emptying After Parietal Cell Vagotomy (Abstr). Gastroenterology, 72:1087, 1977.

Common Bile Duct and Oddi Sphincter Pressure Before and After Endoscopic Papillotomy in Patients with Common Bile Duct Stones

P. FUNCH-JENSEN, A. CSENDES, M.D., F.A.C.S.,* A. KRUSE, M.D., M. J. OSTER, M.D., E. AMDRUP, M.D., PH.D.

From the Departments of Surgical Gastroenterology and Diagnostic Radiology, Arhus Kommunehospital, University of Arhus, Arhus, Denmark

Pressures in the Oddi sphincter and common bile duct were determined before, immediately after and several weeks after endoscopic papillotomy. Fifteen patients were included in the study. Significant decreases in Oddi sphincter and common bile duct pressures were found and the decrease in Oddi sphincter pressure was to some extent dependent upon the length of the papillotomy.

PREVIOUS STUDIES have shown that the Oddi sphincter is a high pressure zone with phasic activity, creating a gradient between the common bile duct and the duodenum.$^{2-4,7}$ The purpose of this study was to evaluate the effect of endoscopic papillotomy on these conditions.

Materials and Methods

Fifteen patients (10 females and 5 males) with a mean age of 66.2 years (range: 39–85) gave their informed consent to be included in this investigation. Six patients were studied before, immediately after and four weeks after endoscopic papillotomy (EPT). Six patients were studied before and immediately after EPT whereas three patients were available only four weeks after EPT.

After an overnight fast the patients were premedicated with 0.5 mg Atropine and 50 mg Pethidine (Mepiridine®). One hour later, immediately before the introduction of the endoscope, 5–10 mg Diazepam was administered intravenously.

A 195 cm long Teflon® catheter with an inner diameter of 1.0 mm was used for manometric examination. The end was closed and a 1 mm circular side hole was constructed 1 cm from the tip. The recording catheter was constantly perfused with sterile 0.88% saline at a rate of 1 ml/minute through a heavy-duty infusion pump (Braun Unita I, West Germany) with greased glass syringe. The catheter was attached to an external transducer (Elema Siemens 746, Sweden) which was connected to a direct writer (Mingograph 82, Elema Siemens, Sweden). The characteristics of this system can be summarized as, low increase in base line pressure (8 mmHg) and a pressure rise rate of 80 mmHg/second after sudden occlusion of the recording hole.

After cannulation of the Ampulla of Vater, the correct position of the recording catheter was checked by gentle aspiration of green bile, directly seen in the endoscope through the transparent Teflon catheter.

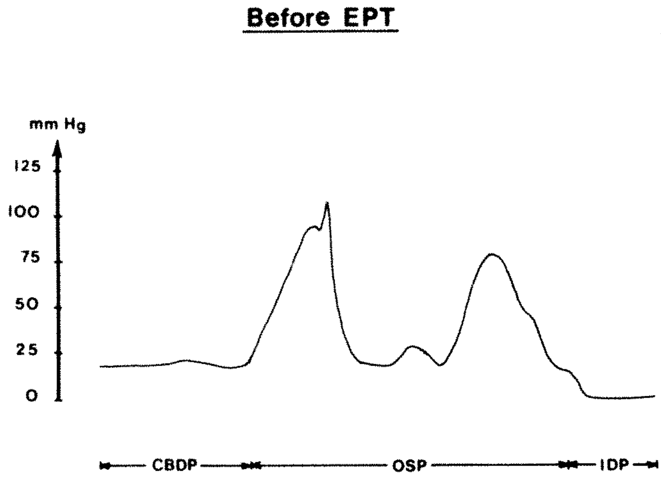


FIG. 1. A tracing from a patient before endoscopic papillotomy (EPT). The common bile duct pressure (CBDP), the Oddi sphincter pressure (OSP) and the intraduodenal pressure (IDP) are shown.

---

* Clinical research assistant, University of Arhus during this study.

Reprint requests: P. Funch-Jensen, Surgical Gastroenterological Department L, Arhus Kommunehospital, DK-8000 Arhus C, Denmark.

Supported by grant number 512-7468 from the Danish Medical Research Council.

Submitted for publication: March 13, 1979.

0003-4932/79/0800/0176 $01.15 © J. B. Lippincott Company

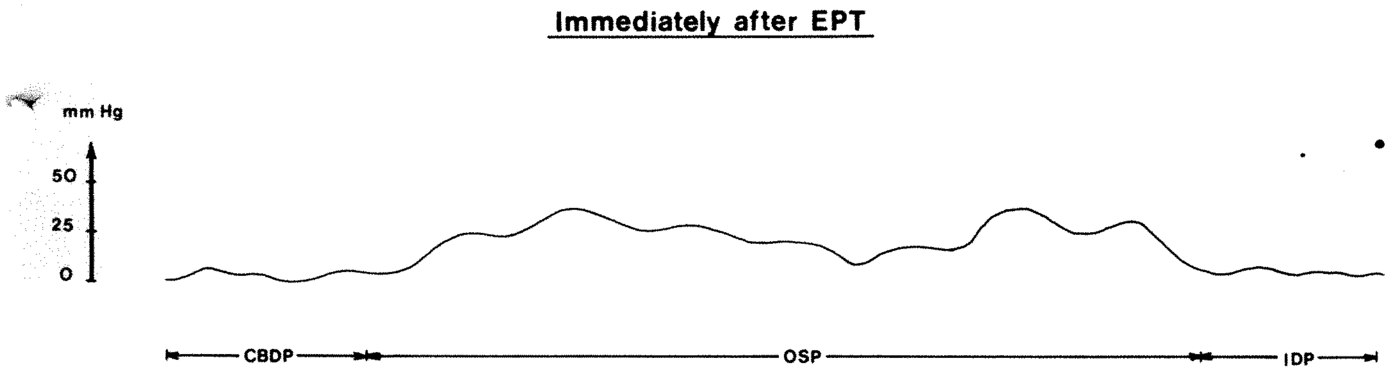


FIG. 2. Tracing from a patient immediately after endoscopic papillotomy (EPT) giving the common bile duct pressure (CBDP), the Oddi sphincter pressure (OSP) and the intraduodenal pressure (IDP).

For the determination of the Oddi sphincter pressure (OSP) the station pull through technique was employed, the recording hole remaining in the same position for several seconds or minutes. The mean OSP is given as the average of peak pressures and the intraduodenal pressure was taken as zero reference in this calculation as well as in the determination of the common bile duct pressure (CBDP).

The Olympus endoscopes JF-B$_2$ and JF-B$_3$ with papillotome were the endoscopes used. In ten patients it was possible to estimate the extension of the papillotomy in millimeters.

All values are given as mean ± standard error of the mean (SEM). For statistical evaluation the Mann-Whitney rank sum test was used and significance was considered at the 5% level.

Results

A tracing before EPT is shown in Figure 1. It can be seen that the Oddi sphincter is a high pressure zone with phasic activity. The effect of EPT upon the OSP is shown in Figures 2 and 3. A significant reduction from 74.4 ± 6.6 mmHg before EPT to 26.3 ± 4.5 and 29.3 ± 8.5 mmHg immediately and four weeks after EPT was found.

Before EPT the mean CBDP was 10.4 ± 1.6 mmHg. A significant reduction to 0 mmHg occurred immediately as well as 4 weeks after EPT (Figs. 2 and 3).

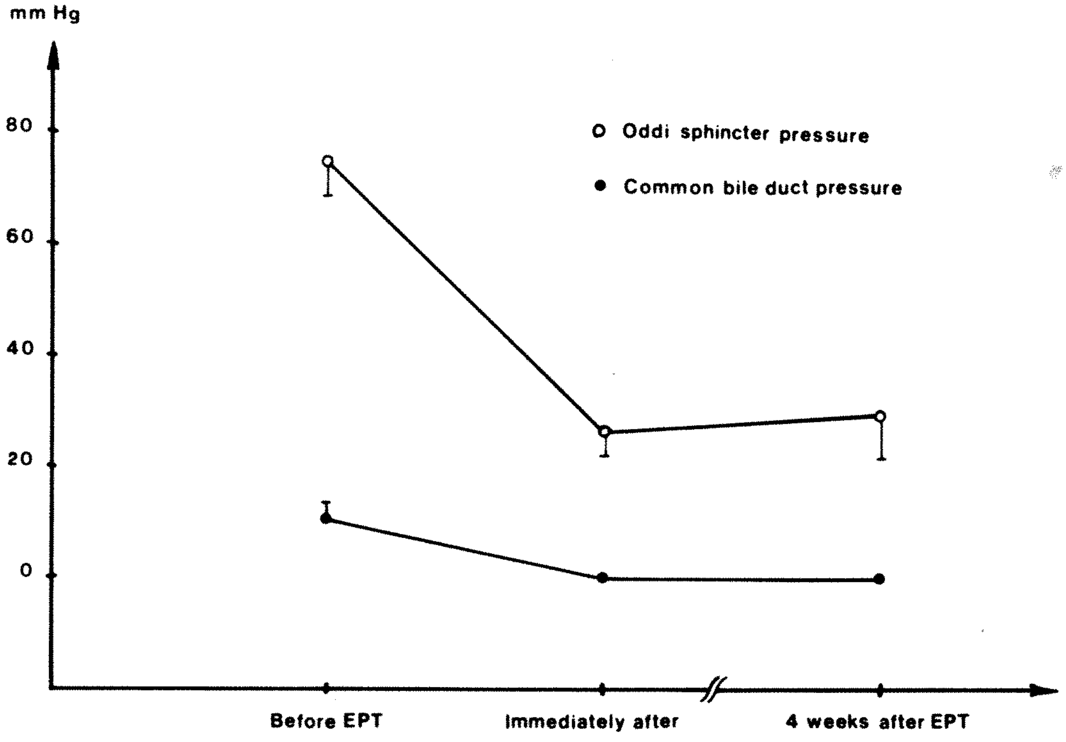


FIG. 3. The mean Oddi sphincter pressure and common bile duct pressure ± standard error of the mean before, immediately after and four weeks after endoscopic papillotomy (EPT).

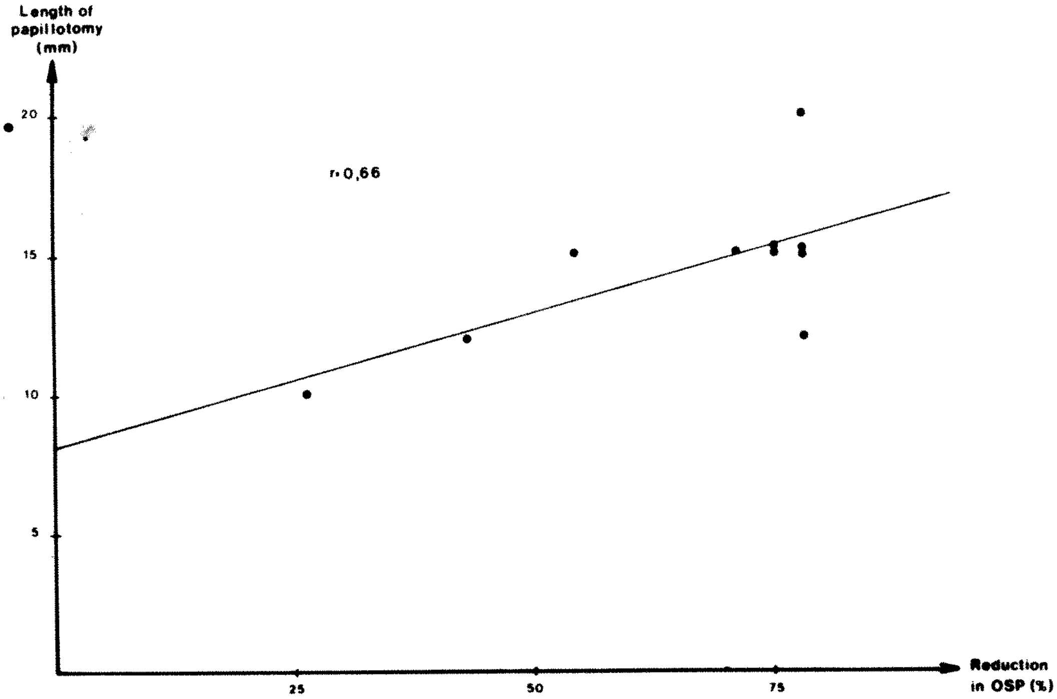


Fig. 4. The regression line showing the correlation between the length of the papillotomy and the reduction in Oddi sphincter pressure (OSP) in per cent. The correlation coefficient (r) was 0.66.

In no tracings were peristaltic activities observed in the common bile duct.

In Figure 4 the reduction in OSP is plotted against the length of the EPT and the regression line drawn. The correlation coefficient was 0.66.

Discussion

This study confirmed previous findings, that the Oddi sphincter is a high pressure zone with phasic activity.[2-4,7]

Endoscopic papillotomy reduced the Oddi sphincter pressure significantly. This is in accordance with the findings of Hogan et al.[5] The magnitude of the reduction in OSP depended, to some extent on the length of the papillotomy.

Under normal conditions, the Oddi sphincter creates a gradient between the common bile duct and the duodenum. This study was in accordance with the findings of Rösch et al.[6] and Hogan et al.,[4] that performing papillotomy, thereby reducing the Oddi sphincter pressure, the choledochoduodenal gradient was equalized, this probably allowing duodenocholedochal reflux.[1]

Acknowledgment

The authors wish to thank Miss Inge Krogh for excellent technical support.

References

1. Bodner, E., Platzer, S., Foedish, H. J. and Schwamberger, K.: Über den Duodenobiliären Reflux nach Totaler Sphincterotomie. Zentralbl. Chir., 99:788, 1974.
2. Csendes, A., Kruse, A., Funch-Jensen, P., et al.: Pressure Measurements in the Biliary and Pancreatic Duct Systems in Controls and in Patients with Gallstones, Previous Cholecystectomy or Common Bile Duct Stones. Gastroenterology, (submitted for publication).
3. Funch-Jensen, P., Csendes, A., Kruse, A. and Øster, M. J.: Common Bile Duct and Oddi Sphincter Pressure in Patients with Common Bile Duct Stones with and without Juxta-ampullar Diverticula of the Duodenum. Scand. J. Gastroenterol., 14:253, 1979.
4. Hogan, W. J., Dodds, W. J., Geenen, J. E., et al.: Sphincter of Oddi Motor Activity in Man: A Zone of Unique Phasic High-pressure Contractions. Symposium on Gastrointestinal Motility, Edinbourgh 1977, paper No 66.
5. Hogan, W. J., Geenen, J. E., Schaffer, R. D., et al.: Sphincter of Oddi Pressure Measurement in Biliary Tract Disease Before and After Endoscopic Sphincterotomy. Gastroenterol. Endoscopy, 23:230, 1977.
6. Rösch, W., Koch, H. and Demling, L.: Manometric Studies During ERCP and Endoscopic Papillotomy. Endoscopy, 8:30, 1976.
7. Øster, M. J., Csendes, A., Funch-Jensen, P. and Skjoldborg, H.: Intraoperative Pressure Measurements of the Choledochoduodenal Junction, Common Bile Duct, Cysticocholedochal Junction and Gallbladder in Patients with Gallstones. Surg. Gynecol. & Obstet. (in press).

Thomas Edison did not simply envision a lamp;
he envisioned a total lighting system.

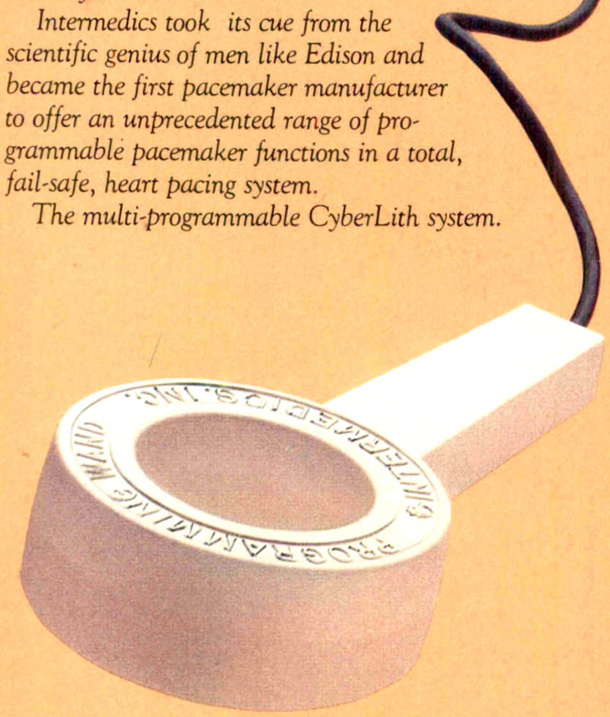
With this same systems orientation,
Intermedics has created not just a new pacemaker,
but a total heart pacing system.

The CyberLith.™ A remarkable new multi-programmabl pacing system.

When Thomas Edison wed his incandescent lamp to a practical electrical distribution network, he created a lighting system that was to revolutionize the way man lived.

Intermedics took its cue from the scientific genius of men like Edison and became the first pacemaker manufacturer to offer an unprecedented range of programmable pacemaker functions in a total, fail-safe, heart pacing system.

The multi-programmable CyberLith system.



The CyberLith provides unprecedented control of heart pacing therapy.

Always maintaining a close relationship with its customers, Intermedics was quick to realize that physicians were demanding greater control in their use of multi-programmable pacemakers. Control that would enable them to respond precisely to their patients' problems.

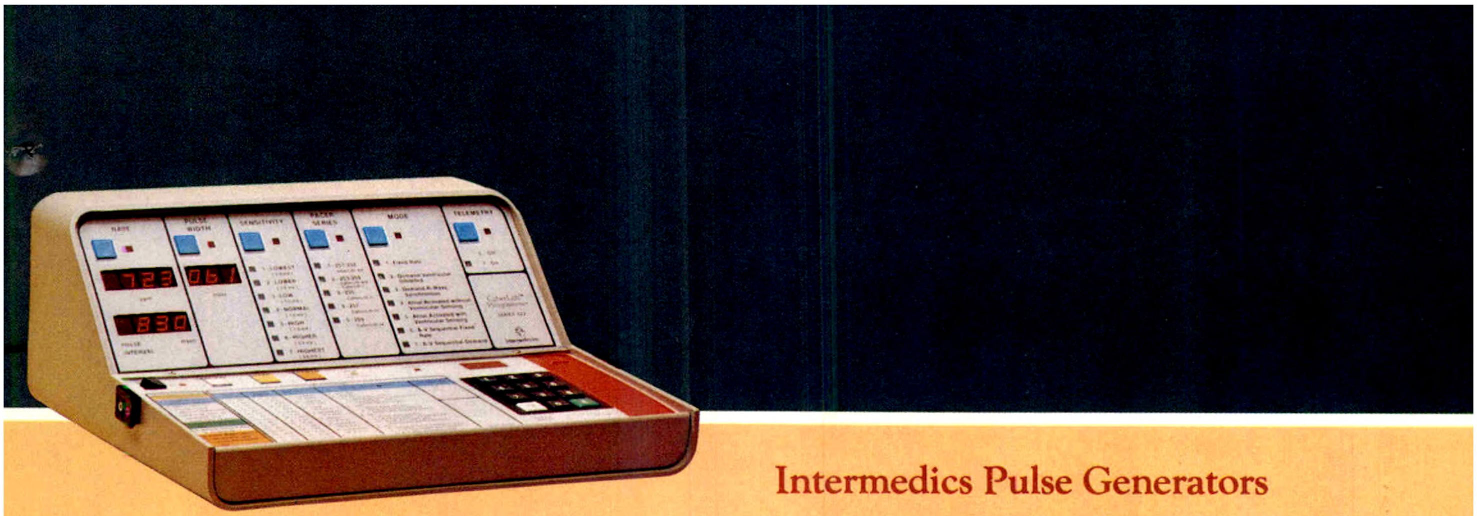
Now, the CyberLith System puts that control in your hands. Our CyberLith (Model 253-05) gives you:

- ***Versatility,*** *with 15 pacing rates ranging from 20 to 120 ppm*
- ***Flexibility,*** *with 15 pulse widths varying from 0.15 to 2.29 mse*
- ***Responsiveness,*** *with 7 sensitivity levels.*
- ***Adaptability,*** *with three operating modes—R-wave inhibite (demand), asynchronous (fixed rate), or R-wave synchrono (demand).*

Fail-safe programming ensures system control.

This unparalleled range of programmable features is made possible by custom CMOS (complementary metal-oxide-semiconductor) integrated circuitry, recognized for its high reliability and low power consumption.

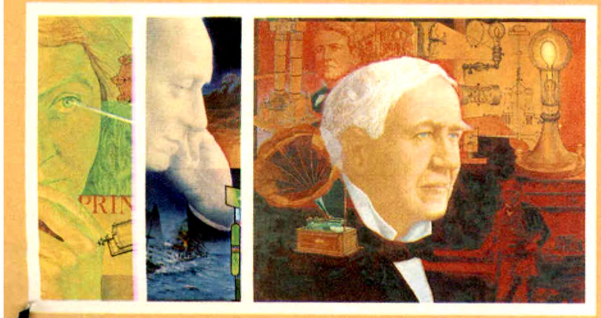
CyberLith functions may be programmed individually or in combination, using a battery-powered portable Programmer. Reprogramming is automatically confirmed, and an advanced fail-safe feature guards against accidental reprogramming.



The CyberLith. A system that Thomas Edison would admire.

Contact your Intermedics Representative for additional information on the many other advantages of our multi-programmable CyberLith Pacing System.

At Intermedics, we are producing tomorrow's technology today, because OUR BUSINESS IS LIFE.



Free limited edition print offer from Intermedics, Inc.

The Thomas Edison original water color is the third in a series by artist Ron Adair, commissioned by Intermedics. A limited-edition print, numbered and signed by the artist, is available to physicians only from Intermedics. To obtain your print, please write to Marketing Administration, Intermedics, Inc., P.O. Box 617, Freeport, Texas 77541.

NOTE: The CyberLith is currently undergoing clinical evaluation and is not routinely available on a commercial basis.

©Intermedics, Inc., June 1979.
CyberLith™ is a trademark of Intermedics, Inc.

Intermedics Pulse Generators

INDICATIONS FOR USE Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation or conduction disorders resulting in symptomatic bradyarrhythmias, tachyarrhythmias, and heart block unresponsive to drug therapy.

PRECAUTIONS Implanted pacemakers have a finite and variable service life as a result of factors such as the initial capacity of the battery and the shelf storage time of the manufactured pacemaker; variations in electrode system resistances, stimulation rate, and the percentage of time the implanted pacemaker is inhibited; and random electronic component failures.

Pacemaker operation can be influenced by electric, magnetic, or electromagnetic energy mimicking normal cardiac activity. In addition, certain environmental sources can couple sufficient energy into a pacemaker system to damage the pulse generator. Specifically, diathermy should not be used on pacemaker patients because of possible total inhibition of the pulse generator; electrocautery can inhibit and/or damage the pacemaker as well as cause burns or possible ventricular fibrillation; defibrillation can damage the pacemaker, and the presence of the pacemaker may cause increased cardiac muscle damage from defibrillation. Microwave ovens that do not exceed federal guidelines for leakage (0.5 W/cm^2 at 2.5 cm from the appliance) will not affect the pacemaker, but leakage in excess of that amount may cause interference. Certain electrical and gasoline-powered appliances can cause inhibition of an implanted cardiac pacemaker system.

For complete precautions, see the Physician's Manual for the Intermedics cardiac pulse generator to be used.

CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

Intermedics Inc.

P.O. Box 617 Freeport, Texas 77541
Tel: (713) 233-8611
Toll free: 1-800-231-2330

Our business is life.

EARLY STAPLE REMOVAL

Staple removal 4 days post-op.

Resulting scar 42 days post-op.

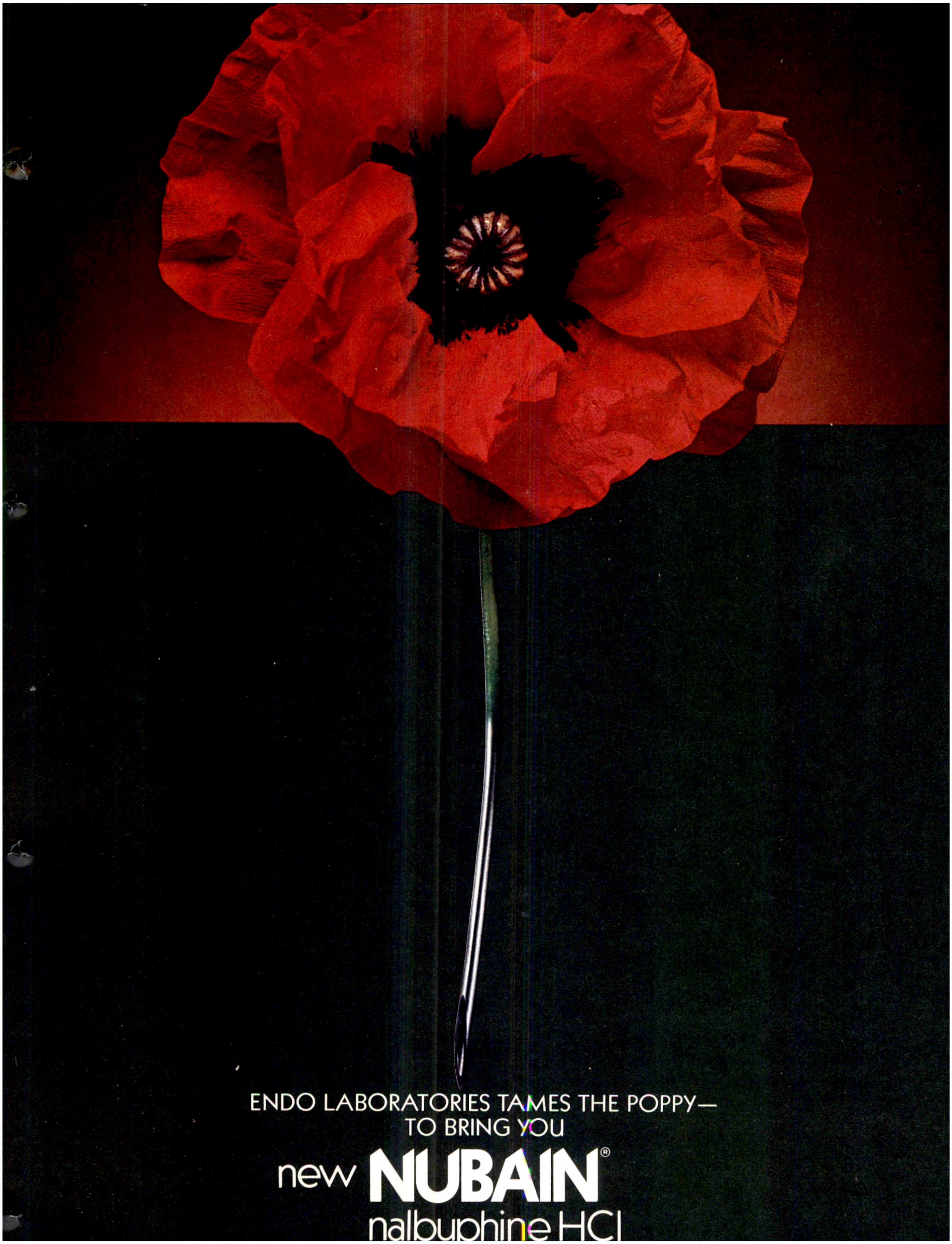
Remove staples early and replace with sterile, reinforce STERI-STRIP® Skin Closures for less chance of infection, a finer scar, greater patient comfort.

Just as with 72-hour suture removal, clinical studies have substantiated that the potential for infection is reduced when staples are removed early and replaced with Steri-Strip Skin Closures. Early staple removal also lessens the chance that adverse cosmetic results will develop from staple puncture marks. Replacing staples early with reinforced Steri-Strip Skin Closures provides greater patient comfort and extended firm support of the wound.

Contact your 3M Surgical Products representative for further information. 3M Surgical Products Division, 3M Center, St. Paul, MN 55101.

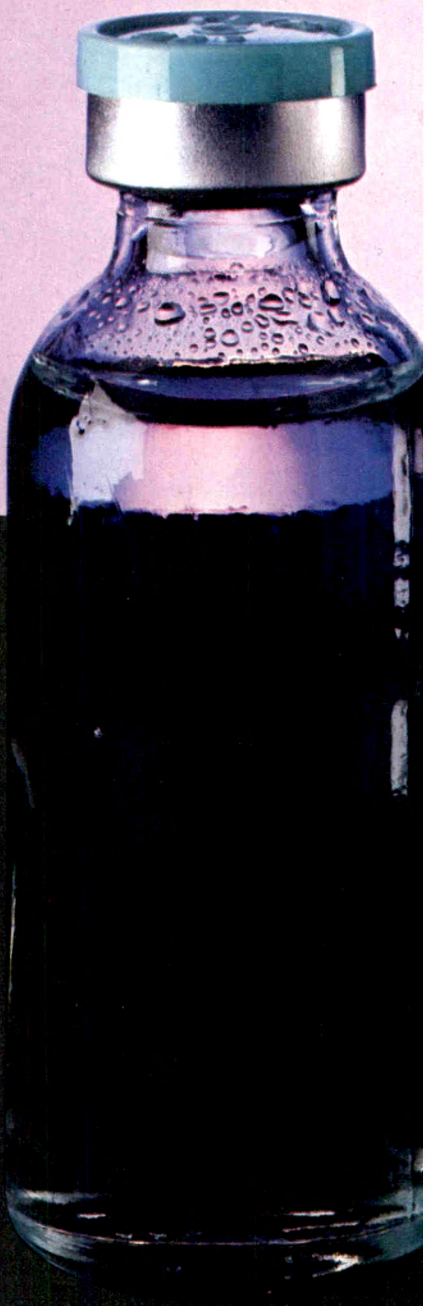
Surgical Products Division/3M
555-IN, 3M Center
St. Paul, MN 55101

QSR-907


ENDO LABORATORIES TAMES THE POPPY—
TO BRING YOU
new NUBAIN®
nalbuphine HCl

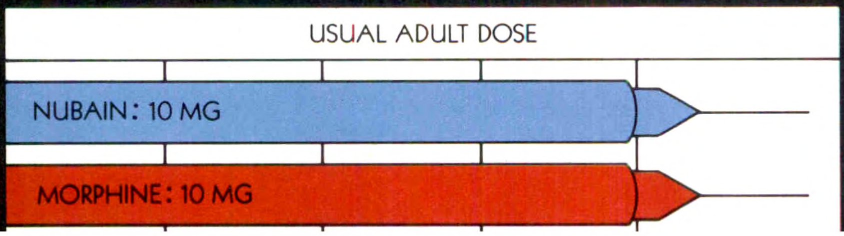
new
NUBAIN® AMPULS AND VIAL
nalbuphine HCl

ANALGESIA COMPARABLE TO MORPHINE



**NUBAIN offers:
onset, peak and duration
comparable to morphine**

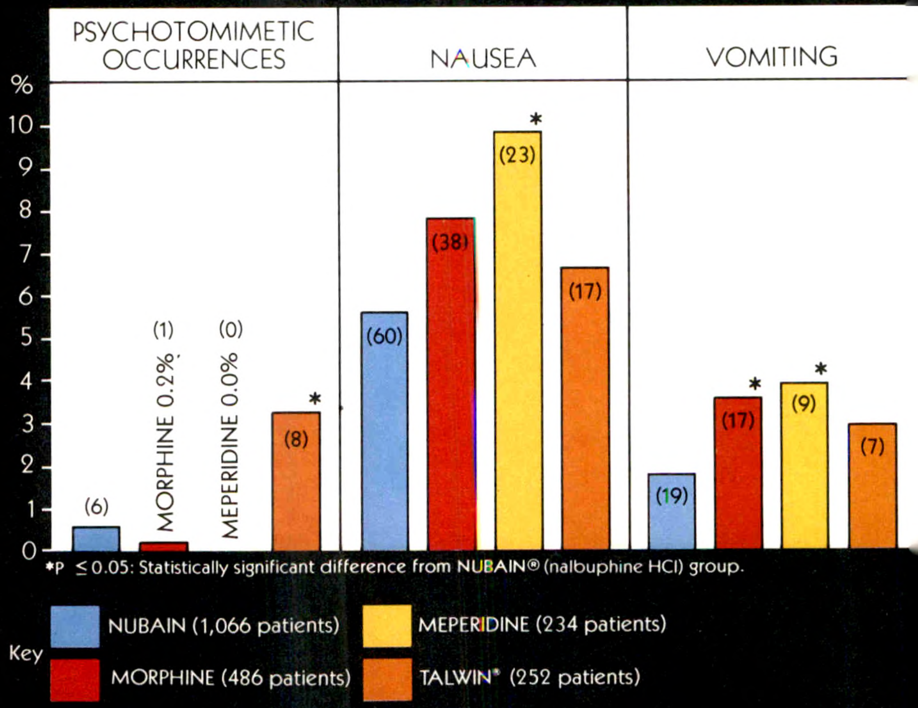
- 10 mg of NUBAIN is comparable in analgesic effect to 10 mg of morphine
- Onset of action with NUBAIN begins within 2 to 3 minutes I.V., and less than 15 minutes I.M. or S.C.
- Analgesic effect of NUBAIN lasts from 3 to 6 hours



WITH A LOW INCIDENCE OF SIDE EFFECTS

Clinical studies show: low incidence of nausea, vomiting and psychotomimetic effects

IN 27 SINGLE OR CROSS-OVER CLINICAL STUDIES (2,038 EVALUATIONS) THESE SIDE EFFECTS WERE OBSERVED:[1]



*P ≤ 0.05: Statistically significant difference from NUBAIN® (nalbuphine HCl) group.

---

1. These clinical studies involved patients with pain from a variety of medical causes, including labor, cancer, and orthopedic and general surgical procedures. Actual number of patients experiencing each side effect is shown in parentheses on the bar graphs. Data on file, Endo Laboratories, Inc.

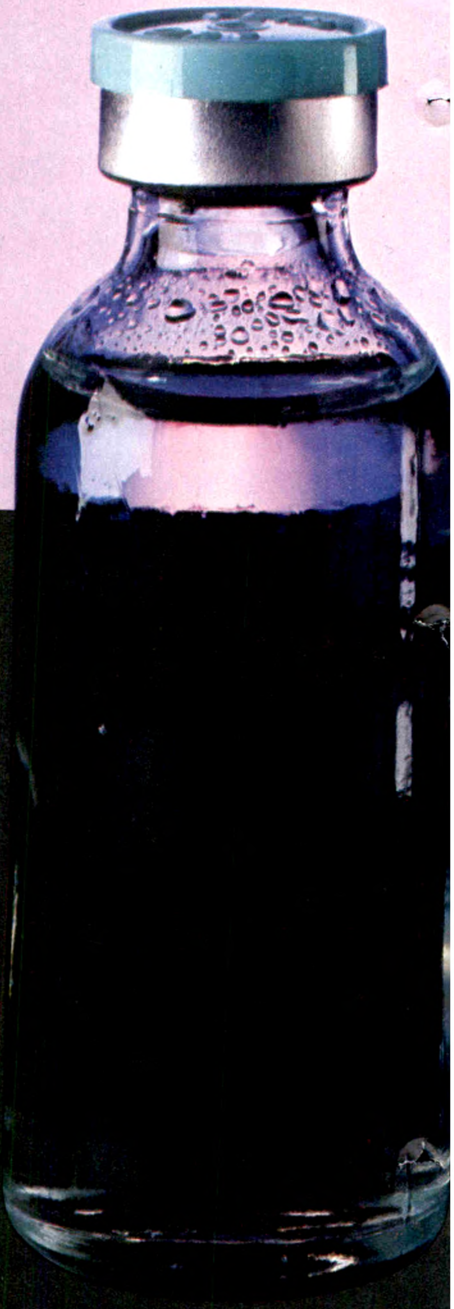
Endo

new

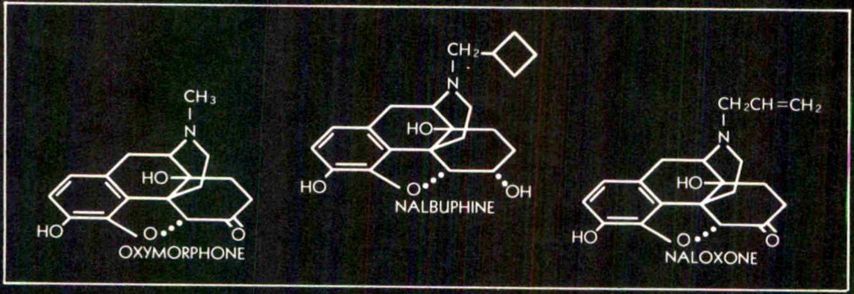
NUBAIN®

nalbuphine HCl

OFFERS LOW POTENTIAL FOR ABUSE



- NUBAIN requires no special storage or additional paperwork beyond your normal order or prescription.
- The unique properties of NUBAIN may be found in its molecular structure.



OXYMORPHONE

NALBUPHINE

NALOXONE

- Certain substances, such as NARCAN® (naloxone HCl), counteract or antagonize the effects and side effects of potent narcotics, such as morphine or NUMORPHAN® (oxymorphone HCl). NUBAIN was designed to incorporate important molecular features of the antagonist NARCAN and the potent analgesic NUMORPHAN, resulting in a drug with strong analgesia but limited abuse potential.

And a lower respiratory effect

- At dosages of 10 mg/70 kg, NUBAIN causes respiratory depression comparable to that of morphine. In contrast to morphine, higher doses of NUBAIN do not increase respiratory depression appreciably (see Precautions).

NARCAN is an Endo registered U.S. trademark.

NUMORPHAN is an Endo registered U.S. trademark.

Please see complete prescribing information on last page of this advertisement.

A clinical summary:

27 investigations evaluated more than 1,000 medical and surgical patients in regard to the effect of NUBAIN upon acute or chronic pain. Among these studies are the following, which highlight important areas of analgesic use:

- ORTHOPEDICS—this study encompassed 52 patients and compared NUBAIN to meperidine. Treatment varied from 1 to 40 days. NUBAIN was found to deliver satisfactory analgesia with no overt evidence of physical tolerance.
- CANCER—this study encompassed 37 patients treated for 1 to 186 days. Many of the patients stabilized on I.M. NUBAIN received dosages every 6-8 hours.
- OBSTETRICS—four double-blind studies were conducted encompassing 159 patients in labor. I.M. NUBAIN was compared to I.M. meperidine. Analgesically, both drugs were deemed similar (10-15 mg NUBAIN equal to 75-113 mg meperidine). Neonates did equally well on both drugs, but there is a possibility that either drug can produce depressive effects in the fetus or neonate. Mothers treated with NUBAIN had fewer side effects, and hospital personnel liked NUBAIN.
- Please see full prescribing information, including a complete discussion of adverse reactions, on following page.

NUBAIN® (nalbuphine HCl)

Analgesia comparable to morphine, with important differences

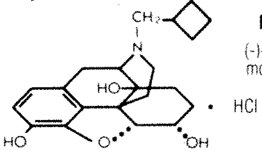
new

NUBAIN®

nalbuphine HCl

DESCRIPTION

NUBAIN (nalbuphine hydrochloride) is a synthetic narcotic agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used narcotic antagonist, naloxone, and the potent narcotic analgesic, oxymorphone.



NALBUPHINE HYDROCHLORIDE

(-)-17-(cyclobutylmethyl)-4, 5α-epoxymorphinan-3, 6α, 14-triol,hydrochloride

Each ml of the injectable aqueous solution of NUBAIN contains 10 mg of nalbuphine hydrochloride.

ACTIONS

NUBAIN is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis.

Its onset of action occurs within 2 to 3 minutes after intravenous administration, and in less than 15 minutes following subcutaneous or intramuscular injection. The plasma half-life of nalbuphine is 5 hours and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours.

The narcotic antagonist activity of NUBAIN is one-fourth as potent as nalorphine and 10 times that of pentazocine.

INDICATIONS

For the relief of moderate to severe pain. NUBAIN can also be used for preoperative analgesia, as a supplement to surgical anesthesia, and for obstetrical analgesia during labor.

CONTRAINDICATIONS

NUBAIN should not be administered to patients who are hypersensitive to it.

WARNINGS

Drug Dependence NUBAIN has been shown to have a low abuse potential which is approximate to that of pentazocine. When compared with drugs which are not mixed agonist-antagonists, it has been reported that nalbuphine's potential for abuse would be less than that of codeine and propoxyphene. Psychological and physical dependence and tolerance may follow the abuse or misuse of nalbuphine. Therefore, caution should be observed in prescribing it for emotionally unstable patients, or for individuals with a history of narcotic abuse. Such patients should be closely supervised when long-term therapy is contemplated.

Care should be taken to avoid increases in dosage or frequency of administration which in susceptible individuals might result in physical dependence.

Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection.

Use in Ambulatory Patients NUBAIN may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, NUBAIN should be administered with caution to ambulatory patients who should be warned to avoid such hazards.

Use in Emergency Procedures Maintain patient under observation until recovered from NUBAIN effects that would affect driving or other potentially dangerous tasks.

Use in Children Clinical experience to support administration to patients under 18 years is not available at present.

Use in Pregnancy (other than labor) Safe use of NUBAIN in pregnancy has not been established. Although animal reproductive studies have not revealed teratogenic or embryotoxic effects, nalbuphine should only be administered to pregnant women when, in the judgement of the physician, the potential benefits outweigh the possible hazards.

Use During Labor and Delivery NUBAIN can produce respiratory depression in the neonate. It should be used with caution in women delivering premature infants.

Head Injury and Increased Intracranial Pressure The possible respiratory depressant effects and the potential of potent analgesics to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, NUBAIN should be used in these circumstances only when essential, and then should be administered with extreme caution.

Interaction With Other Central Nervous System Depressants Although NUBAIN possesses narcotic antagonist activity, there is evidence that in nondependent patients it will not antagonize a narcotic analgesic administered just before, concurrently, or just after an injection of NUBAIN. Therefore, patients receiving a narcotic analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUBAIN may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

PRECAUTIONS

Impaired Respiration At the usual adult dose of 10 mg/70 kg, NUBAIN causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of NUBAIN. Respiratory depression induced by NUBAIN can be reversed by NARCAN® (naloxone hydrochloride) when indicated. NUBAIN should be administered with caution at low doses to patients with impaired respiration (e.g., from other medication, uremia, bronchial asthma, severe infection, cyanosis or respiratory obstructions).

Impaired Renal or Hepatic Function Because NUBAIN is metabolized in the liver and excreted by the kidneys, patients with renal or liver dysfunction may overreact to customary doses. Therefore, in these individuals, NUBAIN should be used with caution and administered in reduced amounts.

Myocardial Infarction As with all potent analgesics, NUBAIN should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Tract Surgery As with all narcotic analgesics, NUBAIN should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

ADVERSE REACTIONS

The most frequent adverse reaction in 1066 patients treated with NUBAIN is sedation (381, 36%).

Less frequent reactions are: sweaty/clammy (99, 9%), nausea/vomiting (68, 6%), dizziness/vertigo (58, 5%), dry mouth (44, 4%), and headache (27, 3%).

Other adverse reactions which may occur (reported incidence of 1% or less) are:

CNS Effects nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine.

Cardiovascular Hypertension, hypotension, bradycardia, tachycardia.

Gastrointestinal Cramps, dyspepsia, bitter taste.

Respiration Depression, dyspnea, asthma.

Dermatological Itching, burning, urticaria.

Miscellaneous Speech difficulty, urinary urgency, blurred vision, flushing and warmth.

DOSAGE AND ADMINISTRATION

The usual recommended adult dose is 10 mg for a 70 kg individual, administered subcutaneously, intramuscularly or intravenously; this dose may be repeated every 3 to 6 hours as necessary. Dosage should be adjusted according to the severity of the pain, physical status of the patient, and other medications which the patient may be receiving. (See Interaction with Other Central Nervous System Depressants under WARNINGS.) In non-tolerant individuals, the recommended single maximum dose is 20 mg, with a maximum total daily dose of 160 mg.

Patients Dependent on Narcotics Patients who have been taking narcotics chronically may experience withdrawal symptoms upon the administration of NUBAIN. If unduly troublesome, narcotic withdrawal symptoms can be controlled by the slow intravenous administration of small increments of morphine, until relief occurs. If the previous analgesic was morphine, meperidine, codeine, or other narcotic with similar duration of activity, one-fourth of the anticipated dose of NUBAIN can be administered initially and the patient observed for signs of withdrawal, i.e., abdominal cramps, nausea and vomiting, lacrimation, rhinorrhea, anxiety, restlessness, elevation of temperature or piloerection. If untoward symptoms do not occur, progressively larger doses may be tried at appropriate intervals until the desired level of analgesia is obtained with NUBAIN.

Management of Overdosage The immediate intravenous administration of NARCAN® (naloxone hydrochloride) is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

The administration of single doses of 72 mg of NUBAIN intramuscularly to eight normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria

HOW SUPPLIED

NUBAIN® (nalbuphine hydrochloride) injection for intramuscular, subcutaneous, or intravenous use (10 mg/ml) is available in:

NDC #0056-0385 10 mg/ml, 1 ml ampuls (box of 10)
NDC #0056-0384 10 mg/ml, 2 ml ampuls (box of 10)
NDC #0056-0386 10 mg/ml, 10 ml vials

Each ml contains 10 mg nalbuphine hydrochloride, 0.1% sodium chloride, 0.94% sodium citrate, 1.26% citric acid anhydrous, 0.1% sodium metabisulfite, and 0.2% of a 9:1 mixture of methylparaben and propylparaben as preservative, pH is adjusted with hydrochloric acid.

6094-1

Rev. March 1979

Endo Laboratories, Inc.
Subsidiary of the DuPont Company
Garden City, New York 11530

DU PONT

NUBAIN is an Endo Registered U.S. Trademark
NARCAN is an Endo Registered U.S. Trademark

Primary Malignant Duodenal Tumors

RAYMOND P. KERREMANS, M.D., JAN LERUT, M.D., FREDDY M. PENNINCKX, M.D.

From the Department of Surgical Gastroenterology,
Academisch Ziekenhuis Sint-Rafaël, University of
Leuven, Belgium

Fourteen patients with primary malignant duodenal tumors are studied. Twelve patients had adenocarcinomas and two patients had malignant lymphomas. Preoperative diagnostic procedures, such as radiographic study of duodenum with hypotonic duodenography, complete duodenoscopy with biopsy and artertiographic studies are discussed. Early diagnosis is the key for curative surgical treatment since these tumors seem to disseminate rather late. In patients with primary duodenal carcinoma the resectability rate was 66.7% —seven Whipple resections and one segmental resection. Only one patient in our series died after a Whipple resection. There was no mortality after other procedures. The five year survival rate was 14.2%. There is a definite correlation between regional lymph node involvement and survival time. The mean survival period after Whipple resection without lymph node invasion is 56.5 months in our series. The survival period after Whipple resection for adenocarcinoma with regional lymph node invasion (6 months) is identical to the survival after palliative internal derivations for duodenal adenocarcinoma (5.8 months). It is concluded that a positive peroperative frozen section of a regional lymph node should exclude resective procedures (except in patients who hemorrhage) because they have a higher mortality rate as derivative procedures. Fifty per cent of the patients treated for malignant duodenal lymphoma is tumor free two years after a radical surgical therapy combined with chemotherapeutical treatment from the early postoperative period.

PRIMARY MALIGNANT duodenal tumors are uncommon. They represent only 0.3% of all gastrointestinal tumors but about 50% of all small intestinal malignancies.[4,7,12]

About 700 instances of malignant duodenal tumors, mostly case reports, are described in the literature.[12] These tumors are usually diagnosed in the latter stages of development because of unclear and intermittent initial symptomatology.[4,5,10] Some patients are initially considered neurotic because of their vague intermittent symptomatology.[4] Symptoms of duodenal obstruction and jaundice are infrequent and depend on the location within the duodenum and also on the characteristics of the tumor itself (growth and size).[2,3,12] The late diagnosis as well as the localization of these tumors make a curative surgical treatment often impossible. Another problem with primary malignant duodenal tumors is the fact that they are frequently grouped together with all other periampullary tumors.[6] In some reports in the literature 56% of the duodenal carcinomas are in fact pancreatic or biliary duct neoplasms.[2]

The purpose of this study is to elucidate the diagnostic and therapeutic aspects, as well as the prognosis of primary malignant duodenal tumors. This will make a comparison with the results obtained in patients presenting small intestinal tumors and other periampullary tumors possible.

Clinical Material

This study reviews 14 patients with primary malignant duodenal tumors. There were nine males and five females between 41 and 70 years included in the study (Table 1). The mean age at laparotomy was 53 years.

The diagnosis was based on pre-, per-, and postoperative data and was always confirmed histologically. Ampulloma's, tumors of the pancreatic head and terminal biliary duct neoplasms were excluded from this series.

Signs and Symptoms

The mean duration of symptoms in our patients was 10.4 months. Four of our patients were treated symptomatically or conservatively for more than one year before admission. In two of these patients a postbulbar and a stress ulcer were primarily diagnosed. Jaundice was seen in ten patients, gastrointestinal hemorrhage, weight loss and epigastric or upper abdominal pain in nine of our patients. One patient with malignant lymphoma presented with a malabsorption syndrome (Table 1).

Diagnostic Studies

The preoperative upper gastrointestinal series were mostly diagnostic. Suggestive images were confirmed

---

Reprint requests: R. Kerremans, Professor of Surgery, Department of Surgical Gastroenterology, Academisch Ziekenhuis Sint-Rafaël, Capucijnenvoer, 35, B-300 Leuven, Belgium.

Submitted for publication: February 20, 1979.

0003-4932/79/0800/0179 $00.70 © J. B. Lippincott Company

TABLE 1. *Primary Malignant Duodenal Tumors*

Pat.	Age, Sex	Dur. Sy.	Ict.	Bleed.	Obstr.	W.L.	Pain	Local.	R.L.N.	Dist. M.	Therapy	Morbidity	Survival
								Adenocarcinoma					
1 CA	47, f	12 m	–	+	–	+	+	II	–	–	WH	Cholangitis	>96 m
2 GM	60, f	2 m	+	+	+	+	–	II	–	–	WH	No	>78 m
3 HE	47, m	9 m	+	–	–	+	–	II	–	–	WH Ant. res.	No Sigm. ca.	30 m
4 BS	51, f	10 m	+	–	–	+	–	II	–	–	WH	No	>22 m
5 MP	60, m	1 m	–	+++	–	–	+	III	–	–	Seg. res.	Jej. fistula	20 m
6 DJ	70, m	4 m	+	+	–	–	+	III	+	–	WH	Pan. fistula	7 m
7 SA	60, f	8 m	–	+++	+	+	+	II	+	+	WH	Pan. fistula	5 m
8 CJ	54, m	1 m	+	–	–	–	+	III	+	–	WH	Sept. perit. Pan. fistula Bronchopn.	Postop.
9 RP	41, m	13 m	+	+	+	+	–	II	+	+	Deriv.	No	11½ m
10 MJ	48, m	4 m	+	–	–	–	+	II	+	+	Deriv.	No	6 m
11 DJ	70, m	1 m	+	++	–	–	+	I	+	+	Deriv.	No	3 m
12 SR	43, f	18 m	+	+	–	+	–	II	+	+	Deriv.	No	3 m
								Lymphoma					
13 CP	44, m	3 m	+	–	–	+	+	dif	+	+	WH + CH	No	>24 m
14 DP	43, m	5 y	–	+	–	+*	+	dif	+	+	DER + CH	No	2 m

W.L.: weight loss.
*: malabsorption.

by hypotonic duodenography. In two patients (14%) the x-ray examination was not conclusive; duodenoscopy with biopsies confirmed the malignancy in these cases. The literature states that upper gastrointestinal studies may be false positive or negative in about 20–30%.[1,7,11,12] Table 2 shows the pathology which, in our opinion, may suggest a duodenal tumor image.

Peroperative Diagnosis and Histology

Adenocarcinoma was found in 12 patients and a malignant lymphoma was found in two patients. In eight patients the adenocarcinoma was localized in the second part of the duodenum (Fig. 1), in three patients in the third part and in one patient in the first part of the duodenum. In both patients with lymphoma, there was a diffuse spread of disease in the duodenum. Fifty per cent of all patients presented distant metastases whereas nine of the 14 patients had local lymph node invasion (65%).

TABLE 2. *Differential Diagnosis in Malignant Duodenal Tumors*

Prolapsing gastric mucosa
Gallbladder dilatation or gallbladder impression by local peritonitis
Postbulbar ulceration
Chronic pancreatitis
Incancerated cholelithiasis with oedematous prolapsing Papilla of Vater
Spec./aspec. duodenal inflammation
Plica longitudinalis
Diverticulum
Periduodenal lymphnode
Retroperitoneal or intramural haematoma following (old) duodenal trauma
Annular pancreas
Brunner gland hyperplasia

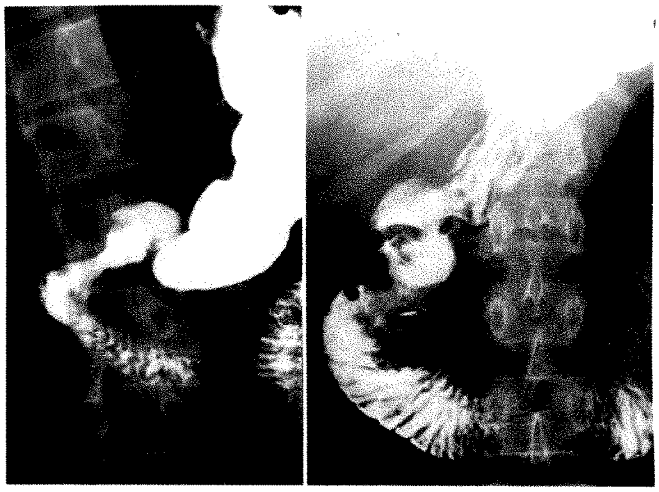


FIG. 1a. X-ray series showing a multinodular infiltrating duodenal process (Adenocarcinoma; Patient 1 in Table 1).

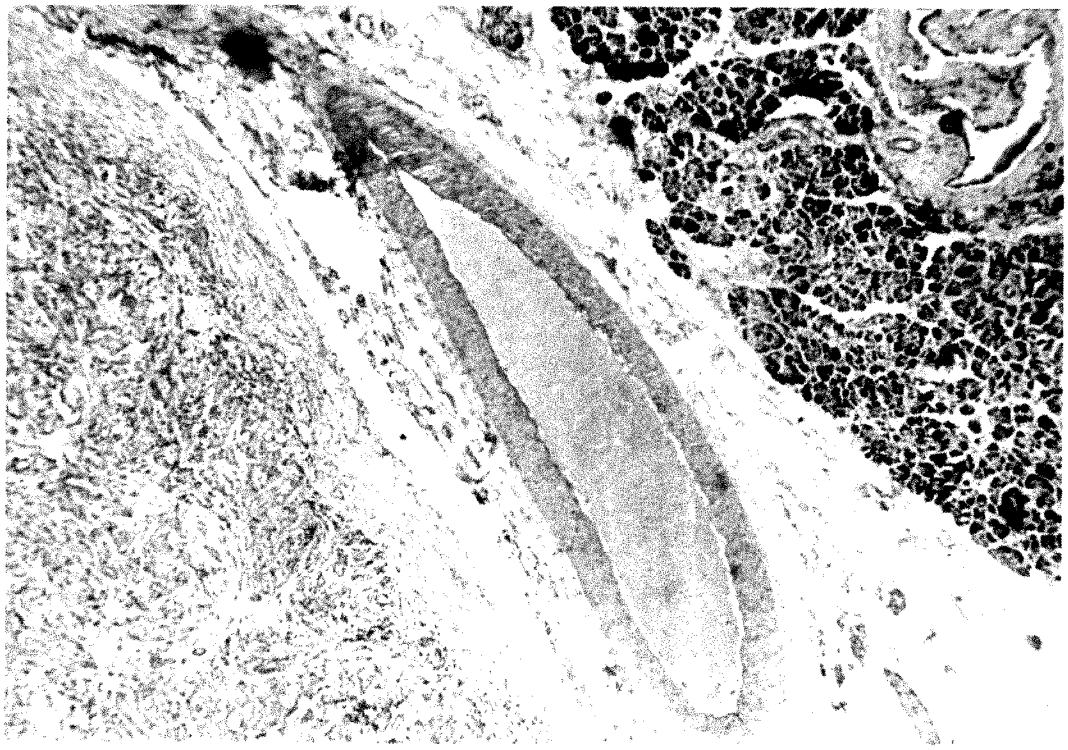


FIG. 1b. Microscopic examination in the same patient. Adventitial tissue separates normal pancreatic tissue on the right from an invasive duodenal adenocarcinoma on the left.

Surgical Treatment

Operative Procedure

We performed a surgical resection in nine of the fourteen patients (64.3%). Eight patients underwent a hemipancreaticoduodenectomy, *i.e.* Whipple resection (six curative and two palliative). A segmental resection of the third part of the duodenum was performed in one patient; in seven of our 14 patients the resection was curative (six Whipple resections and one segmental resection). In the five other patients a gastrointestinal and/or biliodigestive anastomosis was performed.

Additional Treatment

Both cases of malignant lymphoma were additionally treated with chemotherapy which was started during the early postoperative period.

Postoperative Morbidity

The overall postoperative morbidity was 28.5% (4:14 patients). Three pancreatic fistulas were observed after Whipple resection and one jejunal fistula after segmental duodenal resection. One patient (Patient 1) presented recurrent cholangitis, intrahepatic cholestasis and calculus formation caused by stenosis of the hepaticojejunostomy. This patient underwent a hepaticojejunoplasty six years after the Whipple resection.

Postoperative Mortality

One patient (Patient 8) died of a pancreatic fistula, bilateral bronchopneumonia and septic peritonitis 30 days after pancreatoduodenectomy despite reinterventions. The operative mortality of the global series is 7.1% (1:14 patients) and 12.5% in the Whipple series (1:8 patients).

Survival After Surgical Procedures

The mean survival period of the entire group is 23 months (four patients are still alive). Two patients are alive more than five years after surgical treatment (14.2% five year survival rate). The mean survival after Whipple resection for adenocarcinoma is now 39.6 months (three patients alive) and more than 24 months in one patient with duodenal lymphoma (the patient is still alive). The survival period after Whipple resection for adenocarcinoma without regional lymph node involvement is now 56.5 months (three of four patients alive; one patient died six months after resection for sigmoid adenocarcinoma), in contrast with six months (all patients died) after a palliative Whipple resection for duodenal adenocarcinoma.

One patient who underwent a segmental resection of the third part of the duodenum for adenocarcinoma survived 20 months.

Discussion

This study confirms that primary malignant duodenal tumors are often diagnosed late (on average 10.5 months after initial symptoms).[4,5,10] Diagnosis is primarily based on upper gastrointestinal contrast medium radiographic studies. When a duodenal tumor is suspected, a duodenoscopy with biopsy should be performed. This should extend throughout the whole length of the duodenum.[10] Definitive diagnosis should always be confirmed by histological examination. Two years ago we introduced systematically coeliac and superior mesenteric angiographies in all patients proposed for Whipple resection. Resectability, vascular anomalies and the different types of inflammatory or tumerous lesions can be judged by this examination.[1-3] Moreover late radiographic images of the venous filling phase are most important to demonstrate an eventual mesenteric and/or portal vein compression or tumor invasion. In all of our cases the preoperative angiographic findings were confirmed peroperatively. Cavography, although not performed in our series, may also give useful information about tumor invasion. Sonography and CAT-scanning complete the preoperative investigation of these patients.

The resectability of primary malignant duodenal tumors is about 60–70%.[8,9,12] Our 64.3% resectability rate for primary malignant duodenal tumors is much higher than the resectability rate in our series of malignant cephalic pancreatic tumors (20.6%), slightly lower than in our series of primary malignant small bowel tumors (76%) and significantly lower than the resectability rate in our series of ampullomas (88.2%).

The five year survival rate of primary malignant duodenal tumors remains low (10–20%).[8,9,12] The mean survival period after Whipple procedure for primary malignant duodenal tumors is about two years.[8] Some authors report a five year survival of about 40%;[5] however this result has not been confirmed in the literature. In our series we have a mean survival rate of 39.6 months after Whipple procedure. There is a good correlation between the survival period and the presence of regional lymph node involvement. In cases with lymph node invasion the survival period was six months in contrast with 56.5 months in patients without lymph node invasion. Palliative biliary and/or gastrointestinal derivations for primary duodenal adenocarcinoma have a mean survival time (5.8 months) which is comparable with that after Whipple resection in the presence of regional lymph node invasion. These findings as well as the fact that the five year survivals after segmental and Whipple resection are comparable[12] indicate that a Whipple resection should not be performed in the presence of regional lymph node invasion. Consequently, the first step of surgical intervention for duodenal adenocarcinoma should be a frozen section examination of the lymph nodes at the superior mesenteric artery, hepatic artery and truncus coeliacus.

The use of radio- and chemotherapy is confined to malignant lymphomas.[3,9] In one of our patients with a malignant lymphoma there was no further tumor activity two years after a Whipple resection and administration of chemotherapy, despite initial tumoral invasion of the renal capsule.

References

1. Bosse, G. and Neily, J. A.: Roentgenologic Findings in Primary Malignant Tumors of the Duodenum. Am. J. Roentgenol., 107:111, 1969.
2. Cooperman, A. M. and Hoerr, ST. O.: Surgery of the Pancreas. A Text and Atlas. The C. V. Mossby Company, St. Louis, 1978. p. 149.
3. Cortese, A. F. and Cornell, G. N.: Carcinoma of the Duodenum. Cancer, 29:1010, 1972.
4. Hancock, R. J.: An 11-year review of primary tumors of the small bowel including the duodenum. Can. Med. Assoc., 103:1177, 1970.
5. Mason, G. R.: Tumors of duodenum and small intestine. Davis and Christopher (eds.). Textbook of Surgery, Eleventh Edition, Philadelphia, W. B. Saunders Company, 1977.
6. Moreaux, J.: Carcinoma of the Ampulla of Vater: Surgical Aspects: The Sphincter of Oddi. Proc. 3rd Gastroenterology Symp. Nice 1976, pp. 115–119 (Karger-Basel 1977).
7. Moss, W. M., MacCart, D. M., Jules G., et al.: Primary Adenocarcinoma of the Duodenum. Arch. Surg., 108:805, 1974.
8. Nakase, A., Matsumoto, Y., Uchida, K., et al.: Surgical Treatment of Cancer of the Pancreas and the Periampullary Region. Ann. Surg., 185:52, 1977.
9. Sakkar, S. and Ware, C. C.: Carcinoma of the Duodenum: Comparison of Surgery, Radiotherapy and Chemotherapy. Br. J. Surg., 60:867, 1973.
10. Satake, K., Sowam, Yamashita, K., et al.: Carcinoma of the Duodenum: Its Preoperative Diagnosis. Br. J. Surg., 62: 973, 1975.
11. Sedgewick, E. and Sigman, D.: Unusual Lesions of the Duodenum. Surg. Clin. North Am., 56:709, 1976.
12. Spira, I. A., Ghabi, A. and Wolff, W. I.: Primary Adenocarcinoma of the Duodenum. Cancer, 39:1721, 1977.

Major Complications of Small Bowel Diverticula

JOHN W. DONALD, M.D.

Complications of diverticula of the duodenum, jejunum and ileum, exclusive of Meckel's diverticula are extremely rare but can produce major diagnostic and therapeutic problems. Major reported complications include hemorrhage, perforation, biliary and pancreatic obstruction, and inflammation with intestinal obstruction. The mortality of complicated duodenal diverticula is reported from 33 to 48%. Our experience with some of these complications is reported. This experience and a review of other reported cases have led to the following recommendations for surgical treatment. 1) Massively bleeding duodenal diverticulum. Precise localization of the bleeding point by endoscopy and/or arteriography is highly desirable. Excision or partial excision of the diverticulum with suture ligation of the bleeding point is necessary. 2) Perforated duodenal diverticulum. Excision or partial excision, secure closure and drainage are necessary. If peri-Vaterian, a probe should be passed through the ampulla of Vater via the common duct. Unless an entirely satisfactory closure is achieved, complete diversion of the enteric stream from the duodenum by vagotomy, antrectomy with closure of duodenal stump, and Billroth II anastomosis is recommended. 3) Choledochal obstruction due to duodenal diverticulum. Choledocho-duodenostomy. 4) Perforation, bleeding, or obstruction due to jejunal or ileal diverticulum. In rare cases, local excision of the diverticulum is feasible. Usually, resection of the involved segment with primary anastomosis is indicated.

COMPLICATIONS OF DIVERTICULA of the duodenum, jejunum, and ileum, exclusive of Meckel's, are extremely rare but can be serious and produce major problems in diagnosis and management. The complications that have been reported include severe hemorrhage, perforation, biliary and pancreatic obstruction, and inflammation with intestinal obstruction. Other more rare complications such as partial obstruction with malabsorption and blind loop syndrome have been recorded.

Duodenal diverticula are diagnosed in 1–5% of individuals undergoing barium study of the upper gastrointestinal tract. Most occur along the pancreatic border of the second, third and fourth portions of the duodenum which corresponds to the mesenteric border. Jejunal and acquired ileal diverticula also usually arise from the mesenteric border of the small bowel as opposed to the Meckel's diverticulum arising from the antimesenteric border.

The finding of a duodenal or jejunal diverticulum is usually of passing interest only and no clinical significance is suspected. However, the fact that major complications can occur should not be overlooked and one must always be alert to the possibility of these complications and be prepared to perform the appropriate surgical procedure if they are encountered. The precise diagnosis is usually not made preoperatively and at times is difficult to make intraoperatively —especially in the case of perforation or massive hemorrhage from a duodenal diverticulum.

Case Reports

Case 1. A 56-year-old man had sudden severe pain in the right upper quadrant of the abdomen. The patient's pain persisted and required narcotics for partial relief. A few hours later, when examined at hospital admission, the patient had marked tenderness and muscle rigidity in epigastrium and right upper quadrant of abdomen. WBC was 16,600/mm^3 with 52% segmented neutrophiles and 33% stabs. Abdominal x-rays revealed no definite free air. The preoperative diagnosis was perforated duodenal ulcer or acute obstructive cholecystitis, but operative findings revealed a retroperitoneal inflammatory process lateral to the duodenum. The Kocher maneuver and reflection of hepatic flexure of colon enabled us to determine that a perforated duodenal diverticulum in the second portion of the duodenum was the cause of the patient's acute illness. The diverticulum was excised and the defect closed in two layers. The duodenal wall in this area was indurated and friable. A large penrose drain was inserted near the area of the excised diverticulum. On the sixth postoperative day, the patient developed drainage indicative of a duodenal fistula but this closed spontaneously four days later. He also developed a wound infection which responded well to simple drainage. He has remained free of gastrointestinal symptoms for 14 years.

Comment

The retroperitoneal phlegmon lateral to the duodenum was the clue to diagnosis in this patient. The

From the Surgical Service of Mobile Infirmary and the Department of Surgery, University of South Alabama College of Medicine, Mobile, Alabama

---

Reprint requests: John W. Donald, M.D., 192 Louiselle Street, Mobile, Alabama 36607.

Submitted for publication: January 2, 1979.

0003-4932/79/0800/0183 $00.80 © J. B. Lippincott Company

duodenal fistula complication was minimal in this case but because of the high incidence of this in other reported cases, we believe strong consideration should be given to complete diversion of the intestinal stream from the duodenum when one is treating a perforated duodenal diverticulum.

Case 2. The patient, a 70-year-old woman, was admitted to the hospital with severe pain and tenderness in the epigastrium. She had low grade fever and slight leukocytosis. She was treated with nasogastric suction and antibiotics and the symptoms and abdominal signs subsided after three days. A GI series revealed numerous large duodenal diverticula but no definite perforation. Barium enema and intravenous cholangiogram (patient had previous cholecystectomy) were normal. She was discharged on medical management with bland diet and antacids. She continued to have tenderness in upper abdomen and after two weeks, a deep mass could be felt in the epigastrium beneath the upper portion of right rectus muscle and she was readmitted for exploration. Operation revealed a perforated duodenal diverticulum in the second portion of the duodenum, the perforation being confined by adherence to the liver and surrounding inflammatory process. The perforated diverticulum was excised and the defect closed with an inner layer of chromic catgut and outer layer of interrupted silk. The closure was somewhat tenuous due to the inflammatory process and because of this, we elected to completely divert the intestinal stream from the duodenum by vagotomy and antrectomy with Billroth II anastomosis. She had no postoperative complications and has remained well for the past seven years.

Comment

The diagnosis was not made initially in this patient but the development of a tender mass two weeks later led to the exploration and diagnosis. Following excision of the diverticulum and diversion of the intestinal stream from the duodenum, she had no postoperative difficulty.

Case 3. The patient, a 65-year-old woman, was admitted to the hospital with a massive upper GI hemorrhage manifested by shock, hematemesis and black stools. Nasogastric suction revealed dark blood and at times, red blood. Endoscopy was not available at that time but gastric lavage with iced saline and other conservative measures did not stop the bleeding. A total of 4,000 cc of blood was given over an eight hour period because of the rapid blood loss. Emergency operation was performed and after abdominal exploration revealed no definite source of the hemorrhage, a pyloroduodenotomy was done but no bleeding point was found. There was no ulcer but a duodenal diverticulum in the second portion of the duodenum was noted to be filled with fresh blood. This was explored but it was found not to be the source of bleeding. The blood was coming from a more distal point in the duodenum. The hepatic flexure of colon was mobilized and the duodenum reflected to the left. The dissection was continued medially until the second portion of the duodenum and the pancreas could be mobilized superiorly and the third portion of the duodenum visualized. A large diverticulum in the distal duodenum was visualized and was filled with red blood. When opened, there was active bleeding from a small ulcer in the diverticulum. The diverticulum was partially excised and there seemed to be cessation of the bleeding. The duodenal wall was closed with two layers of sutures. Because of the extensive duodenal dissection and the diverticulum in the second portion which had been partially excised, we performed a vagotomy, antrectomy, closure of duodenal stump and gastrojejunostomy. This was a long, difficult operation and 3500 cc of blood were administered to the patient during the procedure. Her postoperative course was complicated by deep venous thrombosis and pulmonary embolism treated with heparin. After approximately 60 days, the patient was discharged but returned one week later with acute acalculous cholecystitis which was treated by cholecystostomy due to her critical condition. A postoperative tube cholecystogram showed no obstruction of the common duct. The cholecystostomy tube was removed and patient was discharged but due to continued drainage of large amounts of bile from the wound she was readmitted four weeks later and reoperation performed. There was an inflammatory mass in the region of the distal common duct and proximal duodenal region. Because of this, we decided to bypass this area by performing a cholecystojejunostomy. The patient recovered and was discharged from the hospital but 10 days later died suddenly, apparently from another pulmonary embolus.

Comment

The inflammatory process in the region of the partially excised nonbleeding duodenal diverticulum in the second portion of the duodenum probably contributed to some of the patient's postoperative difficulty. Although no obstruction of the common duct was noted on tube cholecystogram, we believe the continued drainage of bile from the cholecystostomy wound was related to this. This again emphasizes the extreme care which must be exercised in excising a periVaterian diverticulum (See Discussion).

Case 4. The patient, a 66-year-old woman, had repeated attacks of upper abdominal discomfort, nausea, vomiting and light colored stools. Cholecystectomy for cholelithiasis had been performed seven years prior to admission. Hospital admission and work-up two months before revealed a dilated common duct but no other abnormality. She was readmitted at this time with similar symptoms, occurring approximately every two days. Repeat barium studies revealed a large duodenal diverticulum arising from the postbulbar portion of the duodenal loop. Intravenous cholangiogram again showed a common duct dilated to 2.5 cm (Fig. 1). Bilirubin was not elevated but because of the persistent symptoms and repeated demonstration of a dilated common duct, exploration was advised. The common duct was dilated to 2.5 cm and a large duodenal diverticulum was exposed after performing the Kocher maneuver. Cholangiogram revealed no dye entering the duodenum (Fig. 2) but after an additional injection of 30 cc of dye, a small amount entered the duodenal diverticulum (Fig. 3). We believed the diverticulum was responsible for the intermittent common duct obstruction and we performed a choledochoduodenostomy. The patient's postoperative course was uncomplicated and she has been relieved of her symptoms for the past seven years.

Comment

Although the bilirubin was not elevated, we believe the operative findings indicated the duodenal diverticulum was causing the marked dilatation of the common duct. Rather than the more hazardous direct approach to the diverticulum, we elected to perform a choledochoduodenostomy.

Case 5. A 61-year-old woman developed sudden severe pain in the left side of abdomen opposite the umbilicus and a few hours later, vomited bile stained fluid. She vomited several times and was admitted to the hospital. Slight abdominal distention was noted and there was moderate tenderness in the left side of the abdomen. Abdominal films revealed a moderate amount of small bowel gas with a few air fluid levels. Some gas was present in the colon. The patient was treated with nasogastric suction and observation. During the next 12 hours, there was 3,000 cc of thick bile stained drainage from the nasogastric tube. The patient's abdomen was slightly more distended and the moderate tenderness in the left side of the midabdomen persisted. Repeat abdominal films showed persistent small bowel distention and less colon gas. Surgery was then advised and revealed a high small bowel obstruction due to an inflamed jejunal diverticulum which was adherent to the mesentery of the splenic flexure of colon (Fig. 4).

The inflamed diverticulum was dissected from the mesocolon and resected with closure of the jejunum with an inner layer of catgut and outer layer of interrupted silk. The freeing and excision of this diverticulum relieved the obstruction. She had no postoperative complications and was discharged on the tenth postoperative day.

Comment

This jejunal diverticulitis (because of adherence to the mesocolon) caused jejunal obstruction. Excision of the diverticulum relieved the problem in this patient but resection of the involved segment is more commonly performed.

Case 6. A 23-year-old man had recurrent attacks of abdominal pain for the past two to three years. Abdominal x-rays taken because of the pain two years before present admission showed a few dilated loops of small bowel but the patient's symptoms subsided. The present attack was more severe and prolonged than others. Abdominal examination revealed moderate distention, mild generalized tenderness but most marked in the left lower quadrant. Peristalsis was high pitched and abdominal x-ray films revealed findings compatible with low small bowel obstruction (Fig. 5). Surgical exploration revealed a low ileal obstruction due to an extremely large diverticulum (apparently Meckel's) filled with inspissated vegetable matter which produced angulation and complete obstruction at the point of origin of the diverticulum (Fig. 6). The ileum distal to this was completely collapsed. A resection of approximately 14 inches of small bowel to include the diverticulum with end-to-end anastomosis was performed. The patient had a smooth postoperative course and has had no abdominal complaints since the operation (2 years ago).

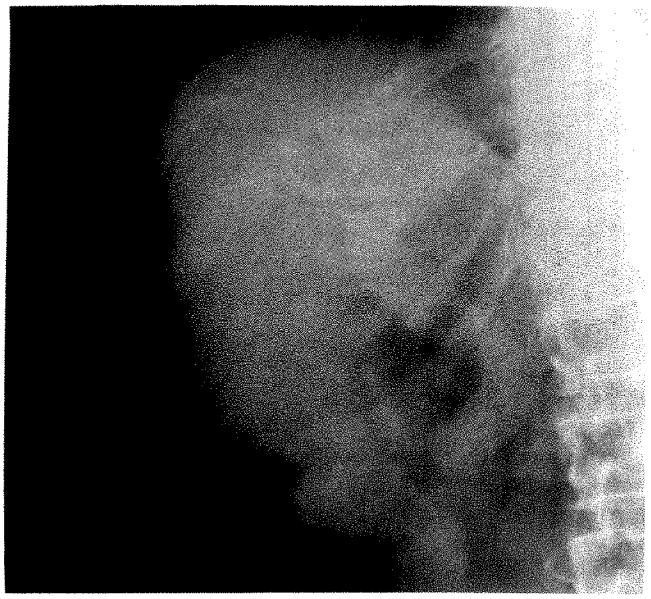


FIG. 1. Case 4. IV cholangiogram showing dilated common duct.

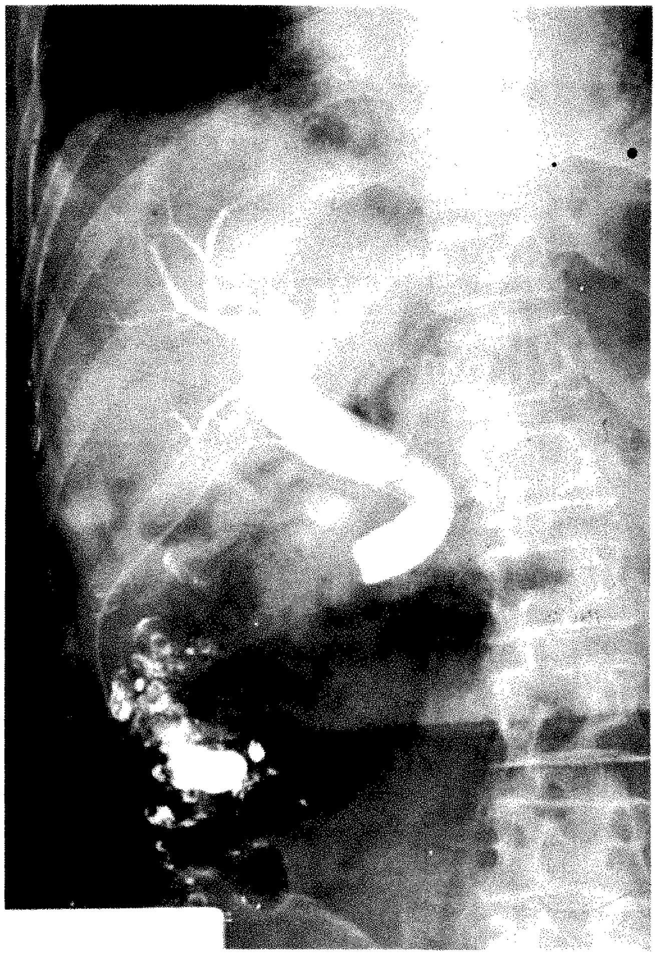


FIG. 2. Case 4. Operating table cholangiogram first injection with no dye entering duodenum.

Comment

Although this was probably a Meckel's diverticulum (not acquired), it is reported because of the unusual finding of intestinal obstruction due to filling of the large diverticulum with inspissated vegetable matter and the angulation at the point of origin of the diverticulum. Resection of this segment of ileum seemed the appropriate procedure in this patient.

Discussion

In 1952, Cattell and Mudge[1] reviewed 25 cases in which elective surgical procedures were done for duo-

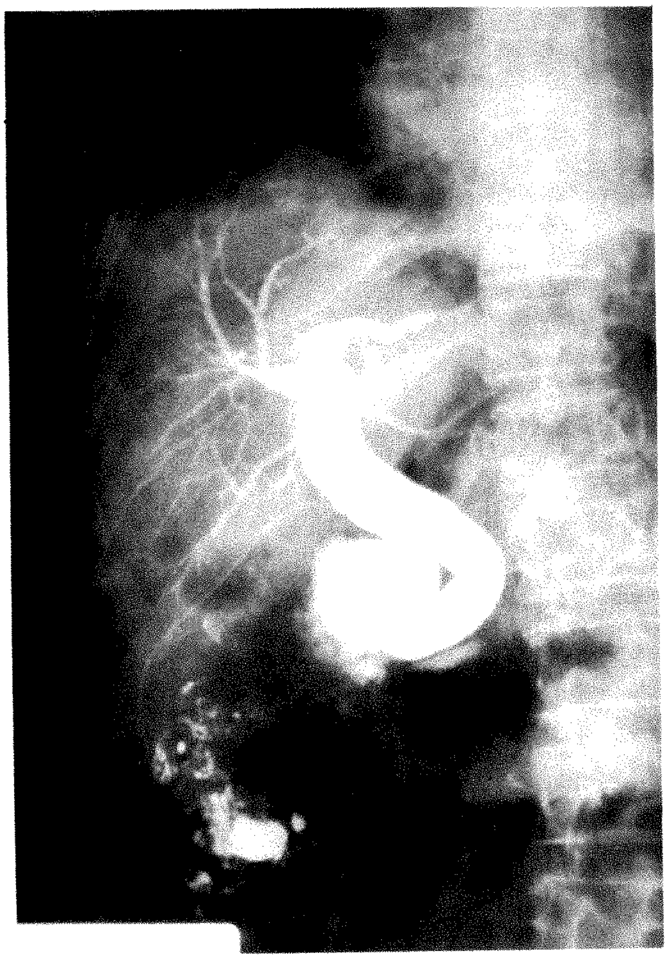


FIG. 3. Case 4. Filling of duodenal diverticulum after additional injection of dye.

denal diverticula at the Lahey Clinic. The diverticulum was excised in 24 of these cases, and his technique for exposure and excision continues today as one to be remembered. Most of these operations were performed for chronic symptoms thought to be due to the diverticulum and were not performed as emergency procedures for major complications. Cattell[1] found that these elective operations were accompanied by a significant mortality (8% in his series), and his results (approximately 50% considered excellent) in relief of symptoms emphasize the difficulty in the selection of nonemergency cases for surgery.

The relationship of biliary tract disease and duodenal diverticula has been pointed out by Landor and Fulkerson[6] in 1966, and the suggestion is made that these diverticula can cause symptoms indistinguishable from biliary calculous disease. Neel[10] has reported two cases of obstruction of the common duct relieved by excision of the diverticulum. Solhang and Semb[15] have reported the operative mortality with excision of the diverticulum as high as 30%—due primarily to duodenal fistula or impairment of pancreatic drainage and resultant complications. They state that until 1960, operations for common duct obstruction due to a duodenal diverticulum have been reported in 14 patients (36% mortality). Excision or invagination with closure of the muscular defect was done in most of these. The authors add one additional case to this series and in view of the high mortality rate of direct surgical approach to the diverticulum, the authors recommend sphincteroplasty rather than excision of the diverticulum.

Willcox[18] has reported nine cases of bile duct obstruction due to duodenal diverticula. Three patients were managed by dilators through common duct, three by duodenotomy and surgical enlargement of the narrow obstructed neck of the diverticulum, and two patients were managed by choledochoduodenostomy.

McSherry and Glenn,[7] in 1970, reported two cases of duodenal diverticula causing biliary tract obstruction and in one of them, the diverticulum was excised. They state that the mechanism of obstruction is twofold. The common duct may drain directly into a diverticulum at the ampulla of Vater which can produce bile stasis, stone formation or infection. The other

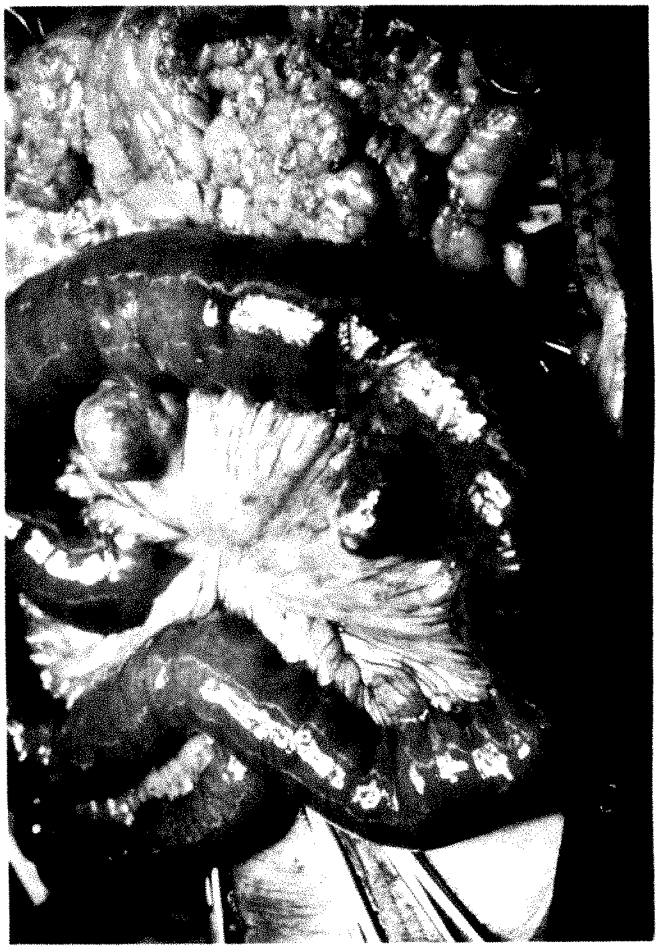


FIG. 4. Case 5. Proximal jejunum after freeing inflammed diverticulum (right) from mesocolon. (Note uninflammed diverticulum on left).

mechanism of obstruction is due to compression of the intraduodenal portion of the common duct by a diverticulum distended with duodenal contents which originates adjacent to the ampulla of Vater. Details of their careful technique in excising the diverticulum are given in their report.

Due to technical difficulties and considerable morbidity and mortality in excision of these diverticula for relief of common duct obstruction, we would recommend choledochoduodenostomy, as was performed in Patient 4. This seems to be a safer procedure and should relieve the common duct obstruction.

In 1961, Zeifer and Goersch[19] reviewed the world literature on perforated duodenal diverticula and added one case. Twenty-two cases were diagnosed and the mortality rate was 48%. They recommended excision of the diverticulum but leaving sufficient cuff at the base to allow turn in of edge without tension. Their other suggestion is that the common duct should be intubated if there is any question about point of entry, and common duct drainage should be performed. Gastrostomy and feeding jejunostomy were also recommended.

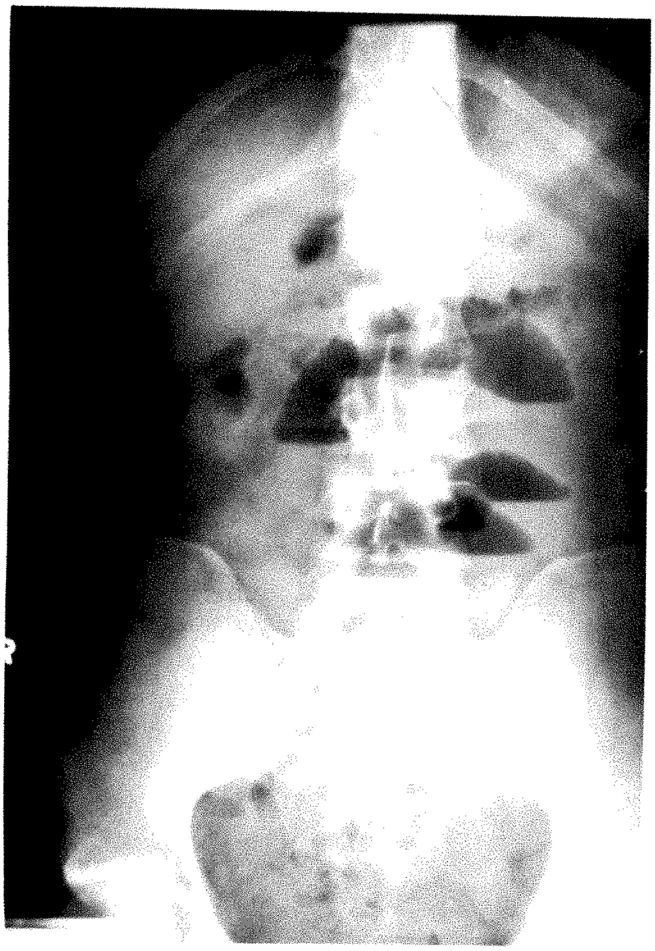


FIG. 5. Case 6. Erect abdominal x-ray showing numerous air-fluid levels and dilated small bowel.

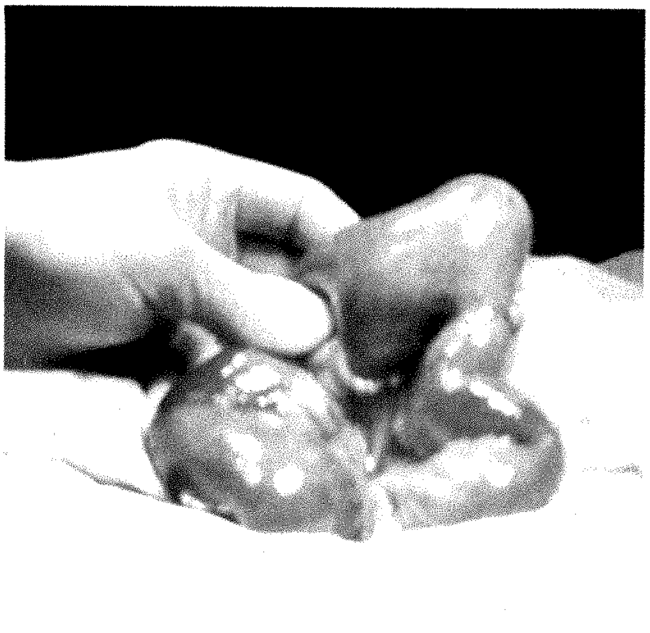


FIG. 6. Case 6. Ileal diverticulum filled with inspissated vegetable matter producing angulation and obstruction.

Others who have reported cases of perforated duodenal diverticulitis include Graves, et al.[3] and Wilkinson and Greaney.[17] Of the five cases reported by Wilkinson and Greaney,[17] there were two deaths. They advise passing a probe or dilator through the ampulla of Vater via choledochostomy to assist in the excision of these periVaterian diverticula. The case reported by Ettman and Kongtawng[2] illustrates perforation of a duodenal diverticulum with coexisting pancreatitis and massive gastrointestinal hemorrhage.

A precise diagnosis at the time of operation is often difficult and it should be emphasized (as has also been mentioned by Wilkinson and Greaney[17]) that retroperitoneal phlegmon lateral to the duodenum is often the only finding until the duodenum is mobilized.

In our cases, the perforated diverticulum was partially excised and closed in one case resulting in a duodenal fistula which closed spontaneously in three to four days. In the other patient, in addition to excision of the diverticulum, vagotomy and antrectomy with Billroth II anastomosis were done without postoperative complication.

Massive hemorrhage from a duodenal diverticulum is extremely rare and the surgical approach is most difficult. Herrington,[4] in 1958, reported a case of successful excision of a massively bleeding diverticulum in the third portion of the duodenum after demonstration of the diverticulum by preoperative barium study. As in Patient 3 in our series, finding the exact source of bleeding and subsequent hemorrhage control can be arduous. Miller, et al.,[8] in 1970, reported eight cases of small bowel diverticula with serious complications. Two of these complications were due to a massively bleeding duodenal diverticulum (one was resected and the other stopped spontaneously). The other six cases were: three common duct obstructions, one perforated duodenal diverticulum, one perforated jejunal diverticulum, and one perforated ileal diverticulum. Three of these eight patients died from complications and there was serious morbidity in two other cases. Munnell and Preston,[9] in 1966, reviewed complicated duodenal diverticula and reported an overall mortality of 33% in 75 cases.

Jejunal diverticula complications are usually due to inflammation and obstruction with occasional localized perforation or hemorrhage. Shackelford,[13] in 1960, reviewed 21 cases of hemorrhage from jejunal diverticula and added three cases. He pointed out that these are acquired diverticula along the mesenteric border and consequently have no muscularis lining. They occur where the blood vessels penetrate the bowel wall and the lack of muscularis exposes the vessel to such an extent that any trauma may cause bleeding.

Perforation of an acquired diverticulum of the jejunum was reported by Herrington[5] in 1962. Nobles,[11] in 1971, reported on 15 patients who underwent jejunal resection for serious complications of jejunal diverticulosis. Five of these patients had intestinal hemorrhage and five others had acute diverticulitis. Three patients were explored for intractable abdominal pain and in both instances, resection of jejunal diverticula corrected the problem. Nobles emphasized that the triad of obscure pain, anemia and dilated loops of jejunum should alert the clinician to the possibility of jejunal diverticulosis.

Obstruction of the distal portion of the small intestine by a concretion that had originated in a jejunal diverticulum was reported by Ottinger and Carter.[12] Two cases of perforated diverticulitis (one in jejunum and one in proximal ileum) have recently been reported by Smith.[14] Viar and Donald[16] have reported three cases of symptomatic jejunal diverticula and two of these had acute inflammation. All were treated by resection.

We encountered two patients with obstruction in our series—one due to an inflamed jejunal diverticulum and one due to a large, most unusual, Meckel's diverticulum with inspissated food particles.

In view of our experience with these cases and from the information presently available, we recommend the surgical management of these complications as follows:

1) *Massively bleeding duodenal diverticulum:* If possible, precise localization of the bleeding point by endoscopy or arteriography and then, after careful exposure, excision or partial excision of the diverticulum with secure control of the bleeding point.

2) *Perforated duodenal diverticulum:* Excision or partial excision, closure, and drainage. If periVaterian, a probe should be passed through the ampulla of Vater via the common duct for protection of the entrance of the duct. Due to the high incidence of duodenal fistula secondary to the inflammatory process and insecure closure, we believe strong consideration should be given to complete diversion of the intestinal stream from the duodenum by vagotomy, antrectomy with closure of duodenal stump, and Billroth II anastomosis.

3) *Common duct obstruction due to duodenal diverticulum:* Because of the hazards of a direct approach to the diverticulum, we believe this complication can be more safely managed by choledochoduodenostomy.

4) *Perforation, bleeding, or obstruction due to jejunal or ileal diverticulum:* In rare cases, local excision of the diverticulum but in most instances, resection of the involved segment with primary anastomosis is preferable.

References

1. Cattell, R. B. and Mudge, T. J.: The Surgical Significance of Duodenal Diverticula. N. Engl. J. Med., 246:317, 1952.
2. Ettman, I. K. and Kongtawng, T.: Massive Gastrointestinal Bleeding and Perforation of a Duodenal Diverticulum with Coexisting Pancreatitis. South. Med. J. 70:761, 1977.
3. Graves, H. A., Durrett, D. W. and Holcomb, G. W.: Perforated Duodenal Diverticulitis. Am. J. Surg., 112:908, 1966.
4. Herrington, J. L.: Massive Hemorrhage Resulting from Benign Ulceration in a Primary Duodenal Diverticulum. Surgery, 43:340, 1958.
5. Herrington, J. L.: Perforation of Acquired Diverticula of Jejunum and Ileum. Surgery, 51:426, 1962.
6. Landor, J. H. and Fulkerson, C. C.: Duodenal Diverticular Relationship to Biliary Tract Disease. Arch. Surg., 93:182, 1966.
7. McSherry, C. K. and Glenn, F.: Biliary Tract Obstruction and Duodenal Diverticula. Surg. Gynecol. Obstet., 130:829, 1970.
8. Miller, R. E., McCabe, R. E., Saloman, P. F. and Knox, W. G.: Surgical Complications of Small Bowel Diverticular Exclusive of Meckel's. Ann. Surg., 171:202, 1970.
9. Munnell, E. R. and Preston, W. J.: Complications of Duodenal Diverticula. Arch. Surg., 92:152, 1966.
10. Neel, H. B.: Obstruction of the Common Bile Duct. Duodenal Diverticular. Minn. Med., 55:1118, 1972.
11. Nobles, E. R.: Jejunal Diverticula. Arch. Surg., 102:172, 1971.
12. Ottinger, L. W. and Carter, E. L.: Obturation of the Ileum by a Jejunal Diverticular Enterolith. Gastroenterology, 68:1596, 1975.
13. Shackelford, R. T. and Marcus, W. Y.: Jejunal Diverticula—A Cause of Gastrointestinal Hemorrhage. Ann. Surg., 151:930, 1960.
14. Smith, J. S.: Jejunal Diverticula—Subtle Cause of Acute Abdomen. Pa. Med., 79:60, 1976.
15. Solhaug, J. H. and Semb, B. K.: Duodenal Diverticulum with Intermittent Biliary Stasis. Acta. Chir. Scand., 140:670, 1974.
16. Viar, W. N. and Donald, J. M., Jr.: Jejunal Diverticulitis. J. Med. Assoc. State Ala., 35:705, 1966.
17. Wilkinson, G. and Greaney, E. M.: Perforated PeriVaterian Duodenal Diverticulitis. Am. J. Surg., 111:351, 1966.
18. Willcox, G. L. and Costopoulos, L. B.: Entry of Common Bile and Pancreatic Ducts into a Duodenal Diverticulum. Arch. Surg., 98:447, 1969.
19. Zeifer, H. D. and Goersch, H.: Duodenal Diverticulitis with Perforation. Arch. Surg., 82:128, 1961.

Review of 404 Patients with Gastrointestinal Fistulas

Impact of Parenteral Nutrition

PETER B. SOETERS,* AMIN M. EBEID, JOSEF E. FISCHER, M.D.†

From the Department of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

This paper represents an extensive review, spanning 30 years of experience with 404 patients with gastrointestinal fistulas. It includes the first period (1945–1960) during the introduction of antibiotics, the second period (1960–1970) which saw rapid improvements in parasurgical care including, respiratory support, perfection of antibiotics, some introduction of nutritional support and improved monitoring, and the third period which saw the introduction of parenteral nutrition specifically central venous hyperalimentation using hypertonic glucose and amino acids (1970–1975) in the treatment of patients with fistulas. The principal causes for mortality in the historical sense were malnutrition, sepsis and electrolyte imbalance. Mortality among patients with gastrointestinal cutaneous fistulas decreased between the first and second periods from approximately 48 to 15%. Surprisingly, mortality did not decrease further in the "hyperalimentation period" although spontaneous closure of gastrointestinal fistulas increased. The results suggest that the improvement in mortality in patients with gastrointestinal cutaneous fistulas is mostly due to the introduction of improved parasurgical care. It is acknowledged that nutritional support was practiced in the 1960's although this was generally not in the form of hyperalimentation. The addition of hyperalimentation in large scale to the treatment of gastrointestinal cutaneous fistulas has improved spontaneous closure and is a valuable part of the armamentarium. The decrease in mortality however, cannot be attributed to parenteral nutrition.

IN 1960, EDMUNDS, Williams and Welch reviewed their experiences with the treatment of 157 patients with gastrointestinal cutaneous fistulas. In this classic paper they called attention to the serious nature and the high mortality of such fistulas and pointed out the relationship between infection, malnutrition, output and mortality. They also stressed that no patient with a high output fistula with malnutrition survived. In 1964, Chapman, Foran, and Dunphy stressed the importance of good nutritional support and reported a decreased mortality of 14% in those patients treated with an excess of 3,000 calories. The mortality rate in those patients in whom 3,000 calories could not be achieved remained high. It was not until the 1970's with the advent of wide spread parenteral nutrition that overall reduction in mortality to the range of 5–20% was achieved in a variety of papers. Since total parenteral nutrition was widely used, it was suggested that this decreased mortality was due entirely to the provision of adequate nutrition to these patients. The relative merits, however, of total parenteral nutrition, as opposed to general advances of fluid and electrolyte therapy, patient management, increased knowledge of respiratory assistance and physiology, acid base balance as well as increased experience with gastrointestinal fistulas was not established.

In order to achieve a perspective on the relative contributions of total parenteral nutrition as opposed to other advances in parasurgical care, we reviewed patients with gastrointestinal fistulas treated at Massachusetts General Hospital for the decade of 1960–1970 and compared the results achieved in this decade with those of 1970–1975 when total parenteral nutrition was widely used in the treatment of such patients. Surprisingly, mortality rates between 1960 and 1970 was a rather low 15%. In this report, therefore, we compare the mortality and other aspects of treatment of two large series of gastrointestinal fistulas treated at one institution by the same group of surgeons with two entirely different techniques. We hope to show that the principles first enunciated by Edmunds, et al., are still applicable to the treatment of gastrointestinal fistulas. Moreover, it is apparent from this report that the general advances in parasurgical care, *i.e.*, fluid and electrolyte therapy, intensive care patient moni-

---

* Department of Surgery, University of Limburg, Maastricht, Holland.

† Department of Surgery, University of Cincinnati Medical Center, Cincinnati, Ohio 45267.

Reprint requests to Dr. Fischer.

Submitted for publication: January 2, 1979.

0003-4932/79/0800/0189 $01.20 © J. B. Lippincott Company

TABLE 1. *Mortality of Patients with External Gastrointestinal Fistulas (1946–1959)*

Gastrointestinal fistulas	(55)	Mortality	62%
Small bowel fistulas	(46)	Mortality	54%
Large bowel fistulas	(56)	Mortality	16%
Overall Mortality	(157)		43.3%

Mortality of all patients with external gastrointestinal fistulas at Massachusetts General Hospital, Boston, U.S.A. from 1947–1960.

toring, acid base balance, etc., have contributed as much or more as total parenteral nutrition to the overall salvage of these patients.

Clinical Material

The records of 247 patients with gastrointestinal fistulas, all those patients seen between 1960 and 1975 were reviewed retrospectively. These were broken down to 119 patients with gastrointestinal fistulas seen between 1960 and 1970, prior to the widespread use of parenteral nutrition and 128 patients treated between 1970 and 1975. Of these 128 patients in the latter series in which hyperalimentation was widely used, 73 of them were treated with total parenteral nutrition. Somewhat surprisingly, the mortality between 1960 and 1970 was found to be 15%, and the overall mortality between 1970 and 1975 was 21%. Analysis of the data will show that the fistula population has changed and that different factors are responsible for the mortality in these two time periods. In addition, we will try to define what role parenteral nutrition has played and does play in the treatment of gastrointestinal fistulas.

1946–1959 Series (157 Patients with External Gastrointestinal Fistulas) Edmunds, et al.,[8]

Overall mortality (Table 1) amounted to 43.3%. The highest mortality was observed in gastroduodenal fistulas (62%) whereas mortality in colonic fistulas was only 16%.

Surgical complications were the direct cause of 67% of these 157 fistulas. The most significant complications of these fistulas were fluid and electrolyte imbalance, malnutrition, and sepsis. These complications largely determined mortality: 78, 61 and 67% respectively. Despite the advent of antibiotics and modern replacement techniques, the results did not present evidence that these techniques contributed to decreased mortality during the 1946–1959 time period. Since surgical complications were the most frequent cause of external fistulas, prevention was considered essential. For this purpose more widespread use of catheter duodenostomy after gastric resection was recommended. Small bowel fistulas generally were high output fistulas, and early surgical therapy by resection of the fistula and the segment of bowel from which it arises was advocated. Fistulas of the lower bowel had a high incidence of spontaneous closure; expectant treatment was satisfactory in many instances.

1960–1970 Series (119 Patients with Gastrointestinal Fistulas)

One hundred nineteen patients were treated during 139 admissions. Fifty-seven patients were male and 62 female. The mean age was 56 years. In case of multiple fistulas, the fistulas were classified according to their site of primary origin. All gastrointestinal cutaneous fistulas were reviewed, from the esophagus to the rectum. No perianal or perirectal fistulas were included. Both internal and external fistulas and combinations of the two were included in the study. Thirty-one patients had internal fistulas only.

Table 2 lists fistula location and primary disease. The primary disease is either the disease giving rise to a "spontaneous" fistula, or the disease for which the patient was operated on. Striking findings are the low number of gastroduodenal fistulas (15 instances of which two were internal) and the large number of external fistulas due to regional enteritis as compared with the 1946–1959 series. In the 1946–1958 series, small bowel internal fistulas associated with regional enteritis were present in only nine patients.

Table 3 lists the cause of the fistula: the disease itself or the operation or a combination of the two. This categorization is arbitrary, but in daily practice, fistulas occur which are clearly spontaneous, and fistulas are caused exclusively by technical perioperative errors. There is an intermediate category, however, where the likelihood of developing a perioperative fistula is greatly enhanced by the severity of the disease. Therefore, we introduced among "operative injuries" operation and disease-fistulas. The surgical procedures which were considered to be the exclusive cause of fistula formation are listed in Table 4. Eight fistulas were caused by operations for ileus and/or adhesions. Only eight fistulas occurred after gastric operations.

Fistula Complications

Through the decades, the three major complications of fistulas have been: electrolyte disturbance, malnutrition, and sepsis, all primary determinants of mortality. Fistula complications are listed in Table 5.

Malnutrition was present in 104 of 119 patients. Moderate malnutrition was defined as total protein of less than 6 g/100 ml and/or weight loss of greater than 7 kg, and was present in 68 out of 119 patients. Severe malnutrition was defined as a total protein of

TABLE 2. *Primary Disease in 119 Patients (1960–1970) with Gastrointestinal Fistulas*

Fistula Location	Total	Cancer	Ulcer	Cholecystitis	Pancreatitis	Diverticulitis	Appendicitis	Adhesions	Trauma	Inflamm. Bowel Disease	Other
esophageal	2	2									
gastric	4	2									2
duodenal	11		5	2	3						1
jejunal	5	1	2					1	1		
ileal	36	11						4		21	
Large bowel											
cecum-ascending	8	5					2				1
transverse	11	8		1						1	1
descending	4							1		1	2
rectosigmoid	29	10				14				3	2
Other											
vesical	1	1									
liver	1								1		
gall bladder	2			2							
pancreas	2				2						
vagina	3	3									
Total	119	43	7	5	5	14	2	6	2	26	9

less than 5 g/100 ml and weight loss of greater than 11 kg and was present in 36 out of 104 patients.

Electrolyte imbalance was present in 54 of 119 patients, and surprisingly, occurred in gastroduodenal, small bowel and large bowel fistulas in about equal numbers.

Infection was divided into two subgroups: wound infection in well draining wounds was listed as controlled infection. Sepsis, intra-abdominal abscesses and peritonitis were categorized as uncontrolled infection. Sixty-six of 119 patients had infection. Of these, 30 were regarded as controlled, and 36 as uncontrolled.

Intestinal obstruction was present in 30 out of 119 patients, a somewhat higher figure than in previous series.

TABLE 3. *Etiology of Gastrointestinal Fistulas in 119 Patients (1960–1970)*

Operative Injuries 86		
Operation and disease		30
appendicitis	2	
duodenal ulcer	1	
pancreatitis	3	
regional enteritis	13	
ulcerative colitis	2	
diverticulitis	7	
others	2	
Operation and cancer		8
Operation and cancer and radiation		5
Unknown		1
Operative injury		27
Suture line failure		15
Spontaneous 33		
Cancer		9
Cancer and radiation		3
Regional enteritis		7
Diverticulitis		6
Granulomatous colitis		2
Ulcerative colitis		1
Peptic ulcer		2
Duodenal ulcer		1
Ruptured cholecystitis		2

Indications for Operation (Table 6)

Persistent drainage of the fistula was the most common single indication (33 times) for operation. In 41 other fistula patients, persistent drainage was associated with other indications, like abscesses, peritonitis, obstruction, bleeding of the primary disease itself: inflammatory bowel disease and malignancy.

Operation (Table 7)

Forty-five patients underwent bowel resection with primary anastomosis. In a large number of these cases, ancillary procedures such as abscess drainage, excision of the fistula, etc, were performed. Eighteen pa-

TABLE 4. *Operations Which Caused Gastrointestinal Fistulas in 119 Patients (1960–1970)*

Gastrectomies	6
Persistent gastrectomies	2
Laparotomies for adhesions and ileus	8
Colostomies	4
Persistent cecostomies	5
Colon resections	3
Pancreatectomies	5
Others	9
Total	42

TABLE 5. *Complications of Gastrointestinal Fistulas in 119 Patients (1960–1970)*

	Total	Esophageal Gastric Duodenal	Small Bowel	Large Bowel	Other
Malnutrition	104				
moderate	68	11	24	29	4
severe	36	3	15	15	3
Electrolyte imbalance	54	11	18	21	4
Obstruction	30	3	15	11	1
Bleeding	4	2	2		
Infection	66				
controlled	30	4	17	9	0
uncontrolled	36	5	15	13	3

tients underwent bypass procedures or external diversion, and 13 patients underwent staged operations. Many of these included external diversion or bypass and abscess drainage in association with a later bowel resection and anastomosis.

A small group underwent comparatively minor procedures such as abscess drainage, excision of the fistula and fistula closure, which are not listed in Table 7.

Patients with resection and primary anastomosis showed the highest closure rate. Forty-three of 45 patients were closed in this way. In contrast, bypass or diversion operations failed to obtain closure in five of 18 patients. Staged operations obtained closure in only six of 13. The number of perioperative complications was significantly lower after resection than after bypass-diversion or staged procedures. Only 12 of 45 patients in the resection group sustained major complications such as infections, anastomotic breakdown, etc. Patients with bypass or diversion operations, however, suffered eight complications in 18 patients. Only two of the 13 patients subjected to staged procedures were free of complications.

Closure (Table 8)

Surgical procedures for closure of the fistula were carried out in 96 of all 119 patients (80.7%). Ultimately, 81 fistulas closed (68.1%). Fifteen were operative failures (12.6%). In 12 patients the fistulas closed spontaneously (10.1%).

Total closure rate, therefore, amounted to 78.2%. No attempt at closure was made in 11 patients (9.2%). Seven of these patients died.

Table 9 shows the closure rates in the light of etiologic factors of primary disease. All but one of the 32 patients with inflammatory bowel disease and diverticulitis were operated for their fistulas. Only two fistulas were not closed. These patients died.

The results were far inferior in patients with fistulas due to carcinoma or operative injuries (Table 9), exhibiting a considerable mortality and low closure rate. Only fistulas due to operative injury had a significant spontaneous closure rate (11 of 42).

Closure rate was lower (67.9%) in the group with high-output fistulas than in low or moderate output groups, but the differences were not statistically significant (Table 10).

Much more significant was the relationship between overall closure rate and sepsis (Table 11): closure was

TABLE 6. *Indications for Operation (1960–1970)*

	Total in Group	No.	Esophageal Gastric Duodenal	Small Bowel	Large Bowel	Other
Persistent drainage alone	74	33	8	8	13	4
with abscess/peritonitis		12		5	5	2
+ obstruction		7	1	5	1	
+ bleeding		1		1		
with obstruction		13		3	8	2
+ ileus		1		1		
+ carcinoma		2			2	
with diverticulitis		2			2	
with gastric ulcer		1	1			
with bleeding		1		1		
with diarrhea and pain		1		1		
Abscess or peritonitis	14	7		4	3	
with obstruction		5		2	3	
with bleeding		2	2			
Obstruction	5	2			2	
with wound dehiscence		1		1		
with diarrhea		2		1	1	
Cancer	3	1			1	
with abscess		1			1	
with obstruction		1			1	
Total	96	96	12	33	43	8

TABLE 7. *Types of Operation, Closure and Complication Ratio (1960–1970)*

	No.	Closure		Complications	
		Yes	Failure	None	Yes
Bowel resection	45	43	2	33	12
Bypass/diversions	18	13	5	10	8
Staged procedures	13	7	6	2	11

often unsuccessful in the presence of uncontrolled sepsis: 16 out of 36 patients with uncontrolled sepsis did not close their fistulas and ultimately died.

Mortality (Table 11)

Eighteen out of 119 patients died (15.1%); 10 of these patients died in the presence of carcinoma. Mortality is higher, but not significantly related to increased output (Table 10). A stronger correlation, however, exists between uncontrolled infection and mortality and is inversely related to closure rate. Of 36 patients with uncontrolled sepsis, 11 died, whereas in the controlled infection and no infection group respectively, zero and seven patients died. Three of these seven patients died with carcinoma. Malnutrition also correlated better with mortality than did output (Table 12). As can be expected from these data, sepsis correlates very significantly with malnutrition, with uncontrolled sepsis often associated with severe malnutrition.

1970–1975 Series (128 Patients with Gastrointestinal Fistulas)

Clinical Material

From 1970–1975, 128 patients with gastrointestinal fistulas were treated at Massachusetts General Hospital, of which 73 were treated with total parenteral nutrition, 36 females, 37 males. Six of these 73 patients had associated internal fistulas. Of the 55 patients with fistulas, (27 females, 28 males) which were not treated with total parenteral nutrition, 25 had associated internal fistulas. Fistula location and the disease which caused the fistula or for which the patient was originally operated on are given in Table 13.

TABLE 8. *Fate of 119 Patients with Gastrointestinal Fistulas (1960–1970)*

Category	No.	Percentage
Surgical procedures	96	80.7
closed operatively	81	68.1
operative failures	15	12.6
Not operated	23	19.3
closed spontaneously*	12	10.1
no closure (7 of these 11 died)	11	9.2

* All but one were operative fistulas.

TABLE 9. *Closure Rates by Etiology/Primary Disease (1960–1970)*

	Inflammatory Bowel Disease	Diverticulitis	Cancer	Operative Injuries
No. of patients	20	12	26	42
Immediate cause				
spontaneous	7	6	12*	—
operative	13	6	14†	42
Fate				
closed (spontaneous)	1	—	—	11
closed (operative)	18	11	17	22
open	1	1	9	9‡
open (not operated)	—	—	5	4
dead	1	1§	7	6

* Includes 3 following radiation.
† Includes 5 patients in whom operation was preceded by radiation.
‡ Four patients had cancer at fistula.
§ Stayed open.

In the group treated with hyperalimentation, gastroduodenal and small bowel fistulas predominate. The underlying etiology involves the surgical complications in the overwhelming majority of those patients treated with hyperalimentation (Table 14). In the nonhyperalimented group, most fistulas were large bowel fistulas and of sponaneous nature (Table 14). Considering the entire group of 128 patients, inflammatory bowel disease and cancer (Table 13) were seen most frequently as the underlying disorder, with gastroduodenal ulcer and diverticulitis also figuring prominently.

Fistula Complications (Table 15)

Complications were categorized using the same criteria as in Table 5. The overwhelming number of patients had controlled and uncontrolled infection; only four patients had no infection. Complications in the nonhyperalimented group were far less numerous, and the incidence of uncontrolled sepsis was significantly lower than in the hyperalimented group.

TABLE 10. *Malnutrition, Electrolyte Disturbances, Closure Rate and Mortality, Related to Fistula Output (1960–1970)*

Output (ml/day)	Malnutrition (Per Cent)	Electrolyte Disturbances (Per Cent)	Closure (Per Cent)	Mortality (Per Cent)
>500 (28 patients)	100	86*	67.9	25
200–500 (32 patients)	84.4	50*	78.1	12.5
<200 (28 patients)	71.4	7.1*	82.1	10.7
Internal	93.6	45.2	83.9	12.5

* $p < 0.01$.

TABLE 11. *Infections, Closure Rate and Mortality (119 Patients, 1960–1970)*

		Fate		
Category	No.	Closed	Open	Death
Infection				
controlled	30	28	2	0
uncontrolled	36	20	16	11
No infection	53	44	9	7
Total	119			

Correlation:closure	
uncontrolled versus no infection	$p < 0.01$
uncontrolled versus controlled infection	$p < 0.01$
controlled versus no infection	p = NS

Indications for Surgical Treatment (Table 16)

In the hyperalimented group intraperitoneal abscesses, adjacent to or secondary to gastrointestinal fistulas, constituted an important indication for operation. In the nonhyperalimented group, a relatively large group were operated on for the primary disease, rather than for the co-existing fistula.

Operation (Table 17)

In most instances resections were performed, especially in the hyperalimented group, because of the high percentage of small bowel fistulas. In the nonhyperalimented group, consisting largely of patients with large bowel fistulas, approximately half of the operations were bypass–diversion, or staged operations. In many instances, in these operations, ancillary procedures were performed such as abscess drainage, fistula resection, etc. In a small group only drainage, fistula closure or fistula resection was performed.

TABLE 12. *Malnutrition, Infection and Mortality (1960–1970)*

Degree of Malnutrition	Total No. Patients	Controlled Sepsis	Uncontrolled Sepsis	No Sepsis	Mortality
Severe	36	7	17	12	10/36 (27.8%)
Moderate	68	21	18	29	7/68 (10.3%)
None	15	2	1	12	1/15 (6.7%)

Results in 128 Patients with Gastrointestinal Fistulas (Table 18)

Fourteen of the patients (29.2%) that were operated in the hyperalimented group died. Of the patients that were not operated in this group, four died. Almost all patients that were operated in the hyperalimented group had their fistulas closed: only two fistulas stayed open.

Thirty-three of the 48 patients that were operated had their fistulas closed, and survived. In the 25 patients that were not operated in the hyperalimented group, 17 closed their fistulas spontaneously, eight stayed open: four of these eight patients died.

In the nonhyperalimented group 40 out of 55 patients were operated. Four patients died. In 35 of these 40 operated patients, fistula closure was achieved, but two of these died; thus 33 out of 40 operated patients closed their fistulas and survived.

Fifteen patients of the 55 were not operated on. In three patients, spontaneous fistula closure occurred. In 12 patients, fistulas stayed open; five of these patients died. Overall mortality in the 128 patients (1970–1975) amounted to 27 (21.1%), 18 (24.7%) in the hyperalimented group, 9 (16.3%) in the nonhyperalimented group.

TABLE 13. *Fistula Location and Primary Disease (1970–1975)*

Fistula Location	Total	Inflam. Bowel Dis.	Cancer	Ulcer	Cholecystitis	Pancreatitis	Diverticulitis	Appendicitis	Peritonitis	Other
Hyperalimented										
Esophageal	2									2
Gastroduodenal	15	1	1	4	1	1				7
Pancr-Biliary	2			1		1				
Small Bowel	43	16	11	2		1	5	1	1	6
Colon & Rectal	11	4	3				1		2	1
Nonhyperalimented										
Esophageal	5	2	1							2
Gastroduodenal	5			4	1					
Pancr-Bil	3	2								1
Small Bowel	9	7	1						1	
Colon & Rectal	33	6	9				10	1		7
Total	128	34	29	12	2	3	16	2	4	26

TABLE 14. *Fistula Location and Primary Etiology (1970–1975)*

Hyperalimented Patients	Esophageal	Gastro-Duodenal	Pancreatic Biliary	Small Bowel	Large Bowel
Surgical complications	2	13	2	35	7
Persistent gastrostomy drainage		1			
Inflammatory disease		1		7	2
Undetermined				2	1
Total	2	15	2	44	10

Nonhyperalimented Patients	Esophageal Gastro-Duod.	Pancreatic Biliary	Small Bowel	Large Bowel
Surgical complications	3		1	6
+ cancer	1	1	1	3
+ diverticulitis				4
+ inflamm. bowel dis.				1
+ stomal ulcer	1			
Inflammatory disease				
Diverticulitis				7
Ulcer disease	2			
Inflamm. bowel disease			7	5
Cholecystitis		1		
Cancer	1	1		7
Trauma	1			1
Total	9	3	9	34

Mortality, Infection and Malnutrition (Table 19)

In the hyperalimented group, 18 patients died. Eleven of these patients had small bowel fistulas. Of these 18 patients, 15 had uncontrolled sepsis; twelve of these patients had pulmonary sepsis. All 12 patients exhibited severe malnutrition and suffered from uncontrolled infection. Four patients died with esophageal–gastroduodenal fistulas. Only one of these patients developed a fistula after an elective procedure for gastroduodenal ulcer disease. Only three patients with colonic fistulas died.

In the nonhyperalimented group uncontrolled infection was also associated with malnutrition and largely determined mortality. Death associated with small bowel fistulas and large bowel fistulas was rare in the nonhyperalimented group. Death associated with esophageal fistulas occurred relatively often in this group: one patient developed a fistula after transthoracic ligation of bleeding esophageal varices, one patient had a bronchoesophageal fistula because of a bronchial carcinoma and one patient developed a fistula after lye ingestion. Only one patient died with duodenal fistula; this patient had carcinoma of the gallbladder.

Discussion

The number of patients with external fistulas admitted during the three time periods was comparable during 1946–1959 and 1960–1970 (Table 20). During 1970–1975, however, a very striking increase in the number of patients treated was observed. This may in

TABLE 15. *Complications of Gastrointestinal Fistulas in 128 Patients (1970–1975)*

	Hyperalimented (73 Patients)					Nonhyperalimented (55 Patients)				
	Esophageal Gastroduod.	Pancreatic Biliary	Small Bowel	Large Bowel	Total	Esophageal Gastroduod.	Pancreatic Biliary	Small Bowel	Large Bowel	Total
Malnutrition	11	3	32	19	65	4	1	3	13	21
Infection										
controlled					30					15
uncontrolled					39					11
Electrolyte imbalance	9	2	21	3	35	2	1	3		6
Obstruction	1	1	3	8	13	1		1	8	10
Bleeding	4	1	6		11		1			1
Wound dehiscence	1	2			3					
Renal failure				1	1					
Jaundice				1	1					

TABLE 16. *Indications for Surgical Treatment* (1970–1975)*

	Esophageal Gastroduod.	Pancreatic Biliary	Small Bowel	Large Bowel
Hyperalimented (73 patients)				
Persistent drainage	2	2	20	5
Intraperitoneal abscess + obstruction	2		15	3
Peritonitis			1	1
Obstruction	1		4	1
Bleeding	2		3	
Disease			1	
Total	7	2	45	10
Nonhyperalimented (55 patients)				
Persistent drainage	2	1	3	14
+ UTI/GUT problems			1	7
Intraperitoneal abscess		1	1	4
Peritonitis			3	
Obstruction			1	5
Disease	2			
Regional enteritis			5	4
Ulcerative colitis				2
Diverticulitis				6
Other	4	1		5
Total	8	4	14	47

* Note: Some patients have more than one indication.

TABLE 17. *Operations for Gastrointestinal Fistulas (1970–1975)*

Type of Procedure	Total	Hyperalimented	Nonhyperalimented
Resection	50	31	19
Bypass/diversion	16	7	9
Staged procedures	7	—	7

part be explained by the increase in the number of patients that were referred to the MGH with existing fistulas. Many of these patients had been hyperalimented at other institutions and failed to close their fistulas: they represent a refractory group, often with uncontrolled sepsis. More aggressive and complicated therapeutic approaches (Table 21) may yield better overall results but may also result in additional complications. Mortality and closure rate (Table 22) improved dramatically during the last two time periods.

1960–1970 Series

It is striking, however, that this decrease in mortality was already achieved in the prehyperalimentation era (1960–1970). It follows that we should be careful in attributing the good results of recent series exclusively to hyperalimentation. We found in the 1960–1970 series that many suggestions put forward in the Edmunds et al. paper proved to be of value.

The low incidence of gastroduodenal fistulas in the 1960–1970 series for instance has eliminated to a large extent these hard to treat high-output fistulas. They will be discussed later in more detail.

Therapeutic results in small bowel fistulas also improved dramatically when compared with the 1946–1959 series. An increasing number of small bowel fistulas were associated with inflammatory bowel disease, often associated with electrolyte disturbances. This did not contribute to mortality however, whereas in the 1946–1959 series, electrolyte disturbances were associated with a mortality of 78%. The time period which elapsed between the genesis of the fistula and the treatment did not correlate with mortality. The fistulas which were due to acute surgical

TABLE 18. *Results in 128 Patients with Gastrointestinal Fistulas (1970–1975)*

	Hyperalimented	Nonhyperalimented
Operative Results	48 Out of 73 Operated (65.8%)	40 Out of 55 Operated (72.7%)
Mortality	14 (29.2%)	4 (10%)
Operative closure	34 (70.8%)—1 died	35 (87.5%)—2 died
Operative success (clos. + alive)	33 (78.8%)	33 (82.5%)
Non-operative Results	25 Not Operated (34.2%)	15 Not Operated (27.3%)
Closed spontaneously	17 (68%)	3 (20%)
Stayed open	8 (32%)	12 (80%)
Mortality	4 (16%)	5 (41.7%)
	Hyperalimented	Nonhyperalimented
Overall mortality	18 (24.7%)	9 (16.3%)
Overall closure + alive	50 (68.4%)	36 (65.4%)

TABLE 19. *Mortality in Relation to Infection and Malnutrition (1970–1975)*

	Hyperalimented (73 Patients)		Nonhyperalimented (55 Patients)		Total (128 Patients)	
Mortality	18 (24.7%)		9 (16.4%)		27 (21.1%)	
Es. gastroduodenal		(17) 4 (23.5%)		(10) 4 (40%)		(27) 8 (29.6%)
Small bowel		(43) 11 (25.6%)		(9) 2 (22.2%)		(52) 13 (25%)
Large bowel		(11) 3 (27.3%)		(33) 3 (9.1%)		(44) 6 (13.6%)
Infection	16		6		22	
Controlled		1		—		1
Uncontrolled		15*		6		21
None		2		3		5
Malnutrition	15		8		23	
Moderate		3		3		6
Severe		12†		5		17
None		3		1		4
Pulmonary emboli	2					
Myocard infarction	1					
Renal failure	2					
Massive bleeding	2					
Malignancy as associated cause of death.	2			4		

* 4–5 of these patients had ongoing sepsis which was not located in the abdomen but was of pulmonary origin.

† All 12 patients with severe malnutrition had uncontrolled infection. In 4 of these patients, pulmonary infection existed.

catastrophe however were generally operated only a few days after discovery, especially when concomitant sepsis existed. When sepsis was well controlled in surgical catastrophe, spontaneous closure occurred relatively often in this group (26%), especially when one takes into consideration that in the 1960–1970 series no deliberate attempt was made to close fistulas conservatively. The period between discovery and operation was generally longer in stable patients without sepsis with fistulas with low output. In these patients, it seems warranted to wait for spontaneous closure, even without hyperalimentation, this mode of treatment not yet being used in the 1960–1970 patients. This approach explains why mortality does not correlate with output in this time period. For the same reason, malnutrition correlates better with uncontrolled sepsis than with output. It is very clear from the 1960–1970 series that uncontrolled sepsis largely determines mortality. It follows that it is a first priority in the treatment of fistulas to convert uncontrolled sepsis to controlled sepsis, especially as the advent of antibiotics did not improve results in the 1946–1959 series.

The clinical picture displayed by patients with internal fistulas resembled a low-output fistula. Closure rate was high (82.1%) in this group. Mortality was low (12.5%). Malnutrition was high (93.6%), but severe malnutrition low compared with other groups (22.6%). In addition, many of these internal fistulas occur in patients with malignant disease or inflammatory bowel disease, which in itself may cause malnutrition.

The data presented herein once again stress the importance of performing resection and end-to-end anas-

TABLE 20. *Patients with External Gastrointestinal Fistulas Treated at the Massachusetts General Hospital*

Period	Patients Treated	Incidence/ Year	Patients Admitted with Existing Fistulas
1946–1959	157	11.2	28%
Jan. '60–Dec. '70	88	8	30.7%
Dec. '70–Jan. '75	97	24.2	50.5%

TABLE 21. *Factors Influencing Fistula Closure in 55 Fistula Patients (1970–1975) without Hyperalimentation*

	Esoph. Gastro-duod.	Pan-creatic Biliary	Small Bowel	Large Bowel	Total
Cancer	1	2	1	4	8
+ radiation	1			4	5
+ chemotherapy				1	1
+ both	1				1
Regional enteritis			4	1	5
+ steroids			3	3	6
Leukemia					
+ radiation				1	1
+ chemotherapy				1	1
+ steroids				1	1
Lupus erythematodes disseminatus					
+ steroids				1	1
Total					30

TABLE 22. *Closure Rate + Mortality (3 Time Periods)*

	Closure Rate (Fistula Closed, Patient Alive)	Mortality
1946–1959		44%
1960–1970	78.2%	15.1%
1970–1975	62.2%	21.1%

TABLE 23. *Fistula Locations in 1960–1970 Series and in Hyperalimented and Nonhyperalimented Groups from 1970–1975*

	Totals 1960–1970	Totals 1970–1975	Hyper-alimented 1970–1975	Nonhyper-alimented 1970–1975
Esophageal	2	7	2	5
Gastroduodenal	15	20	15	5
Pancr-Biliary	4	5	2	3
Small bowel	41	52	43	9
Colorectal	52	44	11	33
Others	5	—		
Total	119	128	73	55

tomoses whenever surgery is undertaken, rather than bypass procedures, partial external diversions and staged procedures. The local situation in the patients in whom bypass or diversion operations were performed may have excluded resection and definitive therapy in some instances. Whenever possible, however, resection and primary anastomosis should be attempted. If this is impossible, total exclusion should be attempted rather than bypass operations or partial exclusions.

The 1960–1970 series has clearly demonstrated that the decreased mortality rate is based upon two aspects:

1) Better patient monitoring including correction of electrolyte disturbances, support of respiratory and cardiac insufficiency.
2) The application of sound surgical principles acquired in the past decades as proposed by Edmunds, et al.[8]

1970–1975 Series

Mortality rates and closure rate still compared very favorably with the 1946–1959 series. Despite hyperalimentation, however, overall closure rate declined and mortality rate increased. Differences were not statistically significant. What was significant was that the advent of hyperalimentation was not associated with an improved closure rate and survival.

It has already been mentioned that the percentage of patients referred to the MGH with existing fistulas increased significantly in the 1970–1975 series. This phenomenon brought about a change in the composition of patient population as reflected in Tables 23–27.

Table 23 demonstrates the increased incidence of fistulas in 1970–1975. This applied especially to the small bowel fistulas. More than half of the patients that were ultimately hyperalimented, were referred with existing fistulas, and these were predominantly small bowel fistulas. Most of these patients had been hyperalimented at other institutions. In the nonhyperalimented group, only a third was referred.

In 1970–1975, a substantial increase in the number of patients with fistulas due to inflammatory bowel disease was observed (Table 24). It is also striking, however, that in the 1970–1975 period, more fistulas[16] due to diverticulitis of the colon were observed than in the longer 1960–1970 period.

Table 25 compares etiology. Apart from the increase in incidence, there seems to be a relative decrease in fistulas due to surgical complications. This is reflected in an increase in spontaneous fistulas due to inflammatory disease which comprises inflammatory bowel disease and diverticulitis, cholecystitis, ulcer disease, etc.

Fistulas of patients that were hyperalimented were in large proportion due to surgical complications (80.8%) whereas in the nonhyperalimented series, only 40% were considered to be caused by surgical complications. It may be significant (Table 20) that the incidence of malnutrition decreased in the 1970–1975 series from 87% (1960–1970) to 51% (1970–1975). This decrease was observed despite the increase in mortality. That it remained so high as it did despite hyper-

TABLE 24. *Primary Disease*

	Total	I.B.D.	Ca	G.D. Ulcer	Chol.itis	Pan.itis	Divertic.	App.	Perit.	Adhes.	Trauma	Other
Total '60–'70	119	26	43	7	5	5	14	2		6	2	9
Total '70–'75	128	34	29	12	2	3	16	2	4			26
Hyperalimented '70–'75	73	21	15	7	1	3	6	1	3			16
Nonhyperalimented '70–'75	55	13	14	5	1	—	10	1	1			10

TABLE 25. *Etiology*

	Total 1960–1970	Total 1970–1975	Hyperalimented 1970–1975	Nonhyperalimented 1970–1975
Surgical complications	86 (72.2%)	81 (63.3%)	59 (80.8%)	22 (40%)
Spontaneous inflammatory disease	21	32	10	22
Ca	12	9	—	9
Others	—	6	4	2
Total	119	128	73	55

alimentation may be explained by the increased incidence in infection, especially in the hyperalimented group. The low incidence of complications in the nonhyperalimented group is based on patient selection: evidently, only patients with major complications like malnutrition or infection were considered for hyperalimentation. It has been previously noted, however, that the nonhyperalimented group largely consisted of large bowel fistulas, many of these being spontaneous in nature.

Electrolyte imbalances were a major problem in the initial series[8] and contributed to mortality in a major way. Electrolyte imbalance did not result in significant mortality in 1960–1970 or 1970–1975.

The increase in infectious complications rate in the 1970–1975 series is also reflected in the large number of patients that were operated for abscesses secondary to fistulas (Table 27). This especially applies to the hyperalimented group, 23 out of 73 patients (31.5%) being operated on for abscesses. The categorization of indications for operation at times may have been arbitrary because it was not always clear from the records if the abscess preceded the fistula or vice versa. Some patients had an abscess drained following surgery, which was an early manifestation of anastomotic breakdown. In Table 27 we list only those abscesses that developed or remained subsequent to the development of a fistula.

The proportion of staged procedures declined even further in the 1970–1975 time period (Tables 7 and 17). In the majority of operations, early resection with or without primary anastomosis was carried out, probably reflecting lessons learned from previous papers.[8]

Table 28 compares overall results in the two later series.

Gastroduodenal Fistulas

Table 29 summarizes the number of patients with gastroduodenal fistulas in three different time periods. The decrease in the number of fistulas after gastrectomy is noteworthy.

From 1960–1975, 19 patients with gastroduodenal fistulas secondary to neoplastic or ulcer disease were treated. Of these, four were internal, (internal fistulas were not considered in the 1946–1959 series) and two were admitted with existing fistulas, and 13 patients developed their fistulas after some type of gastrectomy performed in the MGH. From 1960–1975, 2150 gastrectomies were performed. Therefore, 0.6% of the patients that underwent some form of gastrectomy from 1960–1975 in the MGH developed a gastric, duodenal or gastrojejunal fistula. This incidence is consid-

TABLE 26. *Fistula Complications*

	1960–1970	1970–1975	Hyperalimented 1970–1975	Nonhyperalimented 1970–1975
Total	119 (100%)	128 (100%)	73 (100%)	55 (100%)
Malnutrition	104 (87%)	65 (51%)	44 (60%)	21 (38%)
moderate	68 (57%)			
severe	36 (30%)			
Infection	66 (55.5%)	95 (74%)	69 (94.5%)	26 (47%)
controlled	30 (25%)	45 (35%)	30 (41%)	15 (27%)
noncontrolled	36 (30%)	50 (39%)	39 (53.4%)	11 (20%)
Electrolyte imbalances	54 (45%)	35 (27%)	29 (40%)	6 (11%)
Obstruction	30 (25%)	13 (10%)	3 (4%)	10 (18%)
Bleeding	4 (34%)	10 (8%)	10 (13.7%)	—
Wound dehiscence		4 (3%)	3 (4%)	1 (1.8%)
Renal/hepatic failure		2 (1.6%)	2 (2.7%)	—

TABLE 27. *Indications for Operation**

	1960–1970	1970–1975 Total	1970–1975 Hyper-alimented	1970–1975 Nonhyper-alimented
Persistent drainage + ancillary indication	74	57	29	28
Intraperitoneal abscess + ancillary indication	14	32	23	9

* Only numbers for persistent drainage and abscess drainage are given.

erably lower than the 1.4% reported by Edmunds, et al.,[8] in the 1946–1959 period. This may have contributed significantly to the decrease in mortality that is observed in the later time periods, because these fistulas are hard to treat and exhibit a high mortality. Probably, the main reason for the decreased incidence of fistula formation after gastrectomy is the liberal use of catheter duodenostomies as advocated by Rodkey and Welch.[3,8,9,16,17]

Besides a decreased incidence, a decreased mortality was equally observed in the entire group of esophageal–gastroduodenal fistula patients in the 1970–1975 series (Table 19). Mortality dropped from 62% in 1946–1959 to 40% in the nonhyperalimented patients (1960–1970) to 23.5% in the hyperalimented patients in 1970–1975 suggesting that total parenteral nutrition may have contributed to a decrease in mortality.

Small Bowel Fistulas

Coinciding with the decrease in the relative incidence of gastroduodenal fistulas, an increase in incidence of small bowel fistulas occurred. Fifty-two patients out of a total of 128 had small bowel fistulas. Mortality in this group being a substantial 25%, almost half of all patients dying from fistula disease had small bowel fistulas. Almost all of these patients had uncontrolled infection and some degree of malnutrition which undoubtedly contributed to the high mortality observed. Infectious complications in small bowel fistulas in our material do seem to be less amenable to medical or surgical treatment than fistulas in the proximal or distal gut.

Once local peritonitis exists, resection of a diseased segment containing fistula, etc. does not seem to alleviate infection as often in the small bowel as in other parts of the gut. Anastomoses performed in such areas are inclined to break down, small bowel proximal to diseased resected areas may remain distended and a-functional. In some instances, this leads to a vicious cycle: distension causes permeability of the small bowel, leading to some degree of local peritonitis leading to distension and adynamic ileus, etc. Such patients tend to remain septic, develop sequential organ failure and finally die, despite medical and surgical treatment. At autopsy, general peritonitis and unresolved abscesses are found. Not infrequently, however, findings are less conspicuous, representing bowel distension with sometimes only discrete microscopic signs of chronic inflammation.

Large Bowel Fistulas

Large bowel fistulas, once established, showed far fewer complications than fistulas in other parts of the gut. This is in agreement with previous experiences as reported in the literature.[1,2,10,13–15,18] These fistulas generally are of a low output type and cause little or no malnutrition. In addition, abscesses, peritonitis, etc., if present, are generally localized and amenable to surgical therapy. Obstruction occurred relatively

TABLE 28. *Results of Operative and Non-operative Approaches in the Two Latter Series*

	1960–1970	1970–1975	1970–1975 Hyperalimented	1970–1975 Nonhyperalimented
Operative				
Surg. procedures	96	88	48	40
Closed operatively	81	69 (3*)	34 (1*)	35 (2*)
Failed operatively	15	5	2	3
Mortality	11	18	14	4
Operative success (closure + alive)	81	66	33	33
Non-operative				
Spontaneous closure	12	20	17	3
No attempt at closure	11 (7*)			
Stayed open		20	8	12
Mortality	7	9	4	5
Overall mortality	18 (15.1%)	27	18	9
Overall closure + alive	93 (78.2%)	86 (67.2%)	50	36

* Patients with carcinoma.

TABLE 29. *Gastroduodenal Fistulas (1946–1975)*

	Ca	Ulcer	Chol.itis	Pancr.itis	Other	Total
1956–1959	8	38	2	3	4	55
1960–1970	3	7	2	3	5	20
1970–1975	1 (1 + 0)	8 (4* + 4)	2 (1 + 1)	1 (1 + 0)	8 (8 + 0)	20 (15 + 5)

* Including 2 internal fistulas.
Numbers of gastroduodenal fistulas in three different time periods.

Between brackets, the number of patients that were hyperalimented and were not hyperalimented respectively (1970–1975).

infrequently in this group, but takes longer to develop and are amenable to surgical therapy.

Consequently, mortality in this group improved only slightly in the 1970–1975 series (13.6%) when compared to a mortality of 16% in the 1946–1959 series.

Only 11 out of 44 patients (1970–1975) required parenteral nutrition for malnutrition, largely associated with septic complications.

Three of these 11 patients died (one with intraperitoneal sepsis and pulmonary embolism, one with intraperitoneal sepsis and renal failure, one due to myocardial infarction).

Factors Determining Mortality and the Influence of Parenteral Nutrition

Through the decades, malnutrition, electrolyte disturbances, and sepsis have determined mortality in patients with enterocutaneous fistulas. Malnutrition and electrolyte disturbances were commonly encountered in patients with high-output fistulas. Advances in patient monitoring, correction of fluid and electrolyte imbalance and parenteral nutrition have largely alleviated malnutrition and electrolyte disturbances secondary to high-output fistulas. In the present era, mortality is largely determined by uncontrolled sepsis and sepsis-associated malnutrition (Table 19), as malnutrition in the group of fistula patients that died (Table 19) was in most instances secondary to uncontrolled sepsis. Only very few patients died exclusively of other causes (Table 19).

Parenteral nutrition has been very effective in treating malnutrition when no uncontrolled sepsis coexisted, as no patients were considered to have died from malnutrition alone. However, malnutrition in the presence of uncontrolled sepsis *cannot* be treated by total parenteral nutrition without effective surgical drainage. So long as uncontrolled sepsis persists, the patient's condition deteriorates. Patients get weaker, become passive, cannot clear lung secretions, develop decubitus ulcers, become edematous, develop neurologic disorders, etc., despite parenteral nutrition. Finally, sequential organ failure develops and death ensues.

In conclusion, the one major determinant of mortality in 1970–1975 is uncontrolled sepsis and it is our impression that total parenteral nutrition does not alleviate this problem. On the contrary, papers[1,3,15] reporting excellent results with conservative treatment of fistulas with total parenteral nutrition should be interpreted carefully because the casual reader might get the wrong impression that as soon as a caval catheter is in place, and a glucose-amino acid mixture is administered, he can turn his back on the patient. All authorities would agree, that this is not the proper approach.

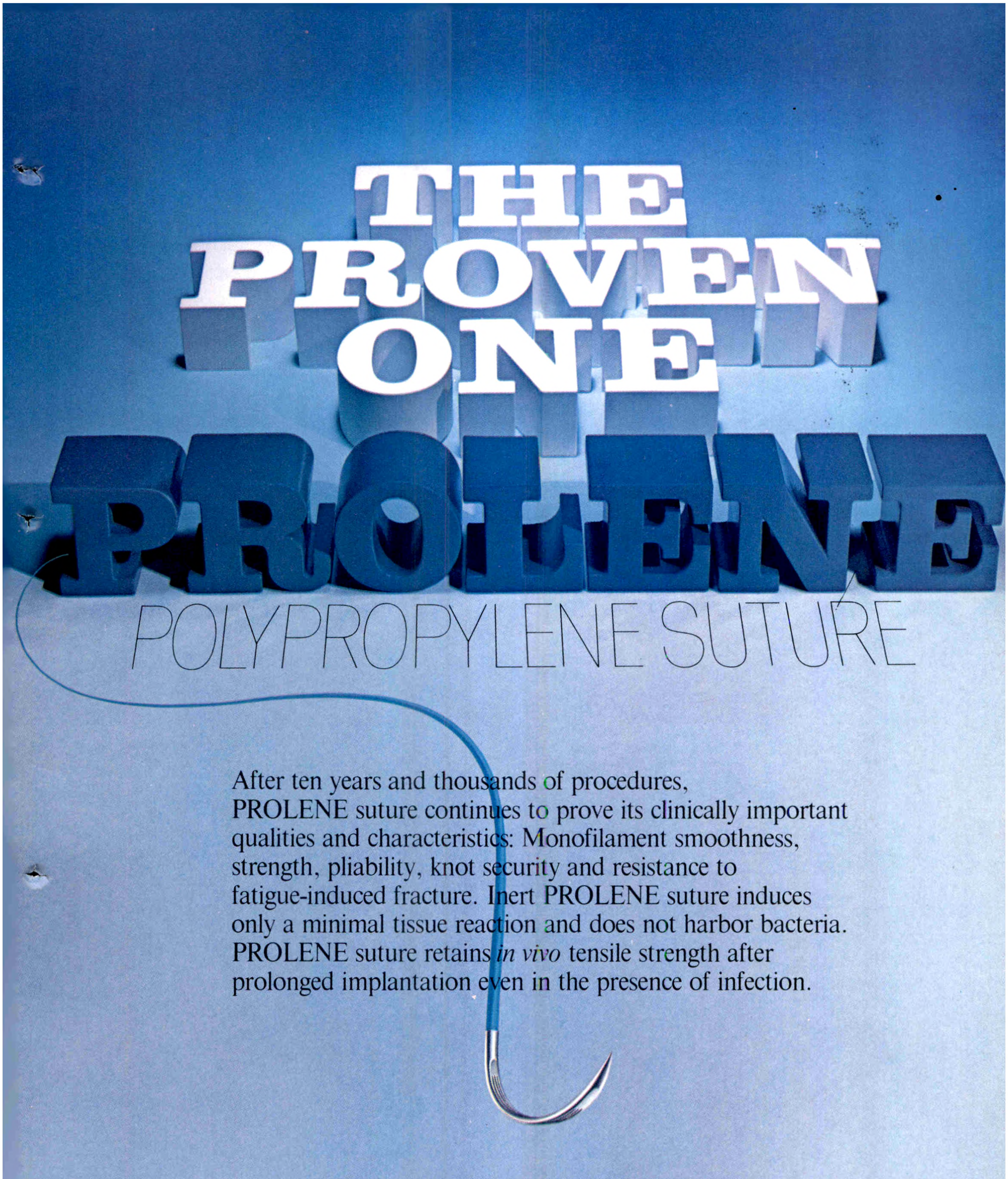
Uncontrolled sepsis should be attacked as early as possible and surgically.[12]

The role of antibiotics remains to be elucidated. Edmunds et al. suggested that antibiotics did not have a major impact on the results during the 1946–1959 era. This impression is confirmed in the two later series. It is our impression from the 1960–1970 and 1970–1975 series that the therapeutic use of antibiotics for intra-abdominal sepsis should be carefully reserved for: septicemia and cholangitis and as preparation for operation. Once signs of intra-abdominal sepsis have occurred, the use of antibiotics do not obviate the necessity to treat the intra-abdominal sepsis surgically.

When sepsis is controlled, or when no sepsis is present, total parenteral nutrition will result in good nutritional status, allowing skin lesions to heal and the future operative field to become quiescent. If spontaneous closure does not occur, operation may then involve less risk than when undertaken in a malnourished patient. Only very few patients died of other causes than uncontrolled infection and associated malnutrition. This demonstrates that total parental nutrition has been effective in treating malnutrition when no uncontrolled sepsis coexisted, because no patients were considered to have died from malnutrition alone. Apart from preparing patients for operation, total parenteral nutrition and bowel rest may achieve spontaneous closure of fistulas. This is most likely to occur when no uncontrolled infection exists, and when we are dealing with well draining lateral fistulas. End fistulas self evidently will not close spontaneously. In addition, distal obstruction, poor condition of the bowel or abscesses adjacent to the fistula constitute reasons for planning a surgical attack on the fistula.[10]

References

1. Aquirre, A., Fischer, J. E. and Welch, C. E.: The Role of Surgery and Hyperalimentation in Therapy of Gastrointestinal-cutaneous Fistulae. Ann. Surg., 180:393, 1974.
2. Ali, S. D. and Leffall, L. D.: Management of Ecternal Fistulas of the Gastrointestinal Tract. Am. J. Surg. 123:535, 1972.
3. Austen, W. G. and Baue, A. E.: Catheter Duodenostomy for the Difficult Duodenum. Am. J. Surg., 160:781, 1964.
4. Bartlett, M. K. and Lowell, W. H.: Acute Postoperative Duodenal Fistula. Am. J. Surg., 218:587, 1938.
5. Bowling, J. W., Hardy, J. D. and Conn, J. H.: External Alimentary Fistulas. Am. J. Surg., 103:6, 1962.
6. Chapman, R., Foran, R. and Dunphy, J. E.: Management of Intestinal Fistulas. Am. J. Surg., 108:157, 1964.
7. Dudrick, S. J., Wilmore, D. W., Vars, H. M. and Rhoads, J. E.: Long Term Total Parenteral Nutrition with Growth, Development and Positive Nitrogen Balance. Surgery, 64:134, 1968.
8. Edmunds, L. H., Williams, G. M. and Welch, C. E.: External Fistulas Arising from the Gastrointestinal Tract. Ann. Surg., 152:445, 1960.
9. Friedemann, M.: Ueber Hilfen und Sicherungen bei gefahrvollen und technisch schwierigen Magenoperationen. Beitr. Klin. Chir., 163:293, 1936.
10. Fischer, J. E.: The Management of High-output Intestinal Fistulas. Adv. Surg., 9:139, 1975.
11. Fischer, J. E., Foster, G. S., Abel, R. M., et al.: Hyperalimentation as Primary Therapy for Inflammatory Bowel Disease. Am. J. Surg., 125:165, 1973.
12. Lorenzo, G. A. and Beal, J. M.: Management of External Small Bowel Fistulas. Arch. Surg., 99:394, 1969.
13. McPhayden, Jr., B. V. and Dudrick, S. J.: Management for Gastrointestinal Fistulas with Parenteral Hyperalimentation. Surgery, 74:100, 1973.
14. Nassos, T. P. and Braasch, J. W.: External Small Bowel Fistulas. Surg. Clin. North Am., 51:687, 1977.
15. Sheldon, G. F., Gardiner, B. N., Way, L. W. and Dunphy, J. E.: Management of Gastrointestinal Fistulas. Surg. Gynecol. Obstet., 51:687, 1971.
16. Welch, C. E.: Surgery of the Stomach and Duodenum. Chicago Year Book, 1955.
17. Welch, C. E. and Rodkey, G. V.: Method of Management of Duodenal Stump after Gastrectomy. Surg. Gynecol. Obstet. 98:376, 1954.
18. West, J. P., Ring, E. M., Miller, R. E. and Burks, W. P.: A Study of the Causes and Treatment of External Postoperative Intestinal Fistulas. Surg. Gynecol. Obstet., 113:490, 1961.



After ten years and thousands of procedures, PROLENE suture continues to prove its clinically important qualities and characteristics: Monofilament smoothness, strength, pliability, knot security and resistance to fatigue-induced fracture. Inert PROLENE suture induces only a minimal tissue reaction and does not harbor bacteria. PROLENE suture retains *in vivo* tensile strength after prolonged implantation even in the presence of infection.

ETHICON

INDICATIONS — PROLENE Polypropylene Suture, U.S.P. may be used wherever Nonabsorbable Surgical Suture, U.S.P. is recommended. Due to its relative biological inertness, it is recommended for use where the least possible suture reaction is desired. As a true monofilament, PROLENE Polypropylene Suture, U.S.P. resists involvement in infection and has been successfully employed in contaminated and infected wounds to eliminate or minimize later sinus formation and suture extrusion. Because of its lack of adherence to tissue, PROLENE Polypropylene Suture, U.S.P., is efficacious as a pull-out suture. **CONTRAINDICATIONS** — There are no known contraindications. **WARNINGS** — Unused PROLENE Polypropylene Sutures which have been removed from their package may be resterilized no more than three times by the standard steam autoclaving method (250°F for 30 minutes) without loss of strength. Unopened suture packages should not be resterilized by steam autoclave. **PRECAUTIONS** — As with other synthetic sutures, knot security requires the standard surgical technic of flat and square ties, with additional throws if indicated by surgical circumstance and the experience of the operator. **ADVERSE REACTIONS** — Transitory local inflammatory reactions have been reported. **SUPPLIED** — Available in U.S.P. sizes, with and without needles, 10/0 thru 2 for pigmented sutures; 7/0 thru 2 for clear.

*Trademark

© ETHICON, INC. 1979

When pain can't wait

Talwin® LACTATE

brand of
pentazocine lactate injection, NF Ⓒ

30 mg parenterally q. 3 to 4 hours.

Pain relief proven:

Clinical proof of efficacy was determined in a wide variety of disease entities.*

Cardiovascular: Of 142 patients, 84% had excellent to good relief.

Gastrointestinal: Of 134 patients (including those with malignancy), 90% had excellent to good relief.

Malignancy: Of 214 patients, 82% had excellent to good relief.

Urology: Of 232 patients, 72% had excellent to good relief.

Miscellaneous: Of 245 patients, 80% had excellent to good relief.

*All doses of Talwin (30 mg Talwin lactate was the most common dose used). Data on file at Winthrop Laboratories.

Over 3/4 billion parenteral doses used worldwide.

Talwin has shown infrequent occurrence of some morphine-like adverse effects such as:

- Severe respiratory depression
- Constipation
- Hypotension
- Urinary retention

While others such as nausea and vomiting are more common.

RARELY REPORTED REACTIONS are those of a psychiatric nature. Even the most acute CNS reactions—hallucinations (usually visual)—have cleared spontaneously within a period of hours. Such patients should be closely observed. In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain. *There have been instances of psychological and physical dependence on Talwin in patients with a history of drug abuse. Such patients should be closely supervised when long-term therapy is contemplated.* **See important paragraph on drug dependence on next page.**

See important product information including warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations, a brief summary of which follows.

Potent—Dependable—Analgesic

Talwin® LACTATE

brand of
pentazocine lactate injection NF Ⓘⓥ

Relieves pain of a moderate to severe nature.

Please consult full prescribing information before prescribing. A summary follows: TALWIN is intended for the relief of moderate to severe pain. 30 mg is usually as effective an analgesic as morphine 10 mg or meperidine 75 to 100 mg. The duration of analgesia may sometimes be less than that of morphine. Analgesia usually occurs within 15 to 20 minutes after intramuscular or subcutaneous injection and within 2 to 3 minutes after intravenous injection. TALWIN is a weak narcotic antagonist with sedative activity. TALWIN may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Hypersensitivity to pentazocine.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on TALWIN in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral TALWIN has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral TALWIN with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for TALWIN in the treatment of the pentazocine abstinence syndrome should be avoided. There have been rare reports of possible abstinence syndromes in newborns after prolonged use of TALWIN during pregnancy.*

In prescribing parenteral TALWIN for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of TALWIN is preferable for chronic administration.

Tissue Damage at Injection Sites. Severe sclerosis of the skin, subcutaneous tissues, and underlying muscle have occurred at the injection sites of patients who have received multiple doses of pentazocine lactate. Constant rotation of injection sites is, therefore, essential. In addition, animal studies have demonstrated that TALWIN is tolerated less well subcutaneously than intramuscularly.

Head Injury and Increased Intracranial Pressure. TALWIN may elevate cerebrospinal fluid pressure. This may be markedly exaggerated in the presence of head injury, intracranial lesions, and a preexisting increase in intracranial pressure. TALWIN may obscure the clinical course of patients with head injuries. TALWIN should be used with extreme caution in such patients and only if its use is deemed essential.

Usage in Pregnancy. Safe use of TALWIN during pregnancy (other than labor) has not been established. Although no teratogenic or embryotoxic effects have been reported in animals, TALWIN should be administered to pregnant patients (other than labor) only when potential benefits outweigh possible hazards; and cautiously in labor of women delivering prematurely.

Acute CNS Manifestations. In therapeutic dosage, rarely, transient hallucinations (usually visual), disorientation, and confusion may occur. Observe such patients carefully and check vital signs. Use caution if the drug is reinstituted since the acute CNS manifestations may recur.

Usage in Children. Not recommended under the age of 12.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Myocardial Infarction. Caution should be exercised in the intravenous use of pentazocine for patients with acute myocardial infarction accompanied by hypertension or left ventricular failure. Data suggest that intravenous administration of pentazocine increases systemic and pulmonary arterial pressure and systemic vascular resistance in patients with acute myocardial infarction.

Precautions: The possibility that TALWIN may cause respiratory depression should be considered in treating patients with bronchial asthma. TALWIN should be used with caution and in low dosage to patients with respiratory depression, severely limited respiratory reserve, respiratory obstruction, cyanosis, renal or hepatic dysfunction. Caution should also be used with patients prone to convulsive disorders and those about to undergo biliary surgery. Patients previously given narcotics, including methadone, may experience withdrawal symptoms after receiving TALWIN.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Dermatologic Reactions: Soft tissue induration, nodules, and cutaneous depression can occur at injection sites. Ulceration (sloughing) and severe sclerosis of the skin and subcutaneous tissues (and, rarely, underlying muscle) have been reported after multiple doses.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received TALWIN during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face, toxic epidermal necrolysis.

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg intravenously or 60 mg intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg.

See Warnings in package insert as to recommended sites and routes of administration. Use subcutaneously only when necessary because of possibility of severe tissue damage at injection sites. For frequent intramuscular injections, note need for rotation of sites as described.

Patients in Labor. A single, intramuscular 30 mg dose has been most commonly administered.

CAUTION: TALWIN should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: Oxygen, parenteral naloxone, intravenous fluids, vasopressors, assisted or controlled ventilation, and other supportive measures should be employed as indicated.

How Supplied: *Uni-Amp®—Individual unit dose ampuls of 1 ml (30 mg)* NDC 0024-1924-04, *1½ ml (45 mg)* NDC 0024-1925-04, *and 2 ml (60 mg)* NDC 0024-1926-04 in boxes of 25.

Uni-Nest™ ampuls of 1 ml (30 mg) NDC 0024-1924-14, *1½ ml (45 mg)* NDC 0024-1925-14, *and 2 ml (60 mg)* NDC 0024-1926-14 in boxes of 25.

Each 1 ml contains pentazocine lactate equivalent to 30 mg base and 2.8 mg sodium chloride, in water for injection.

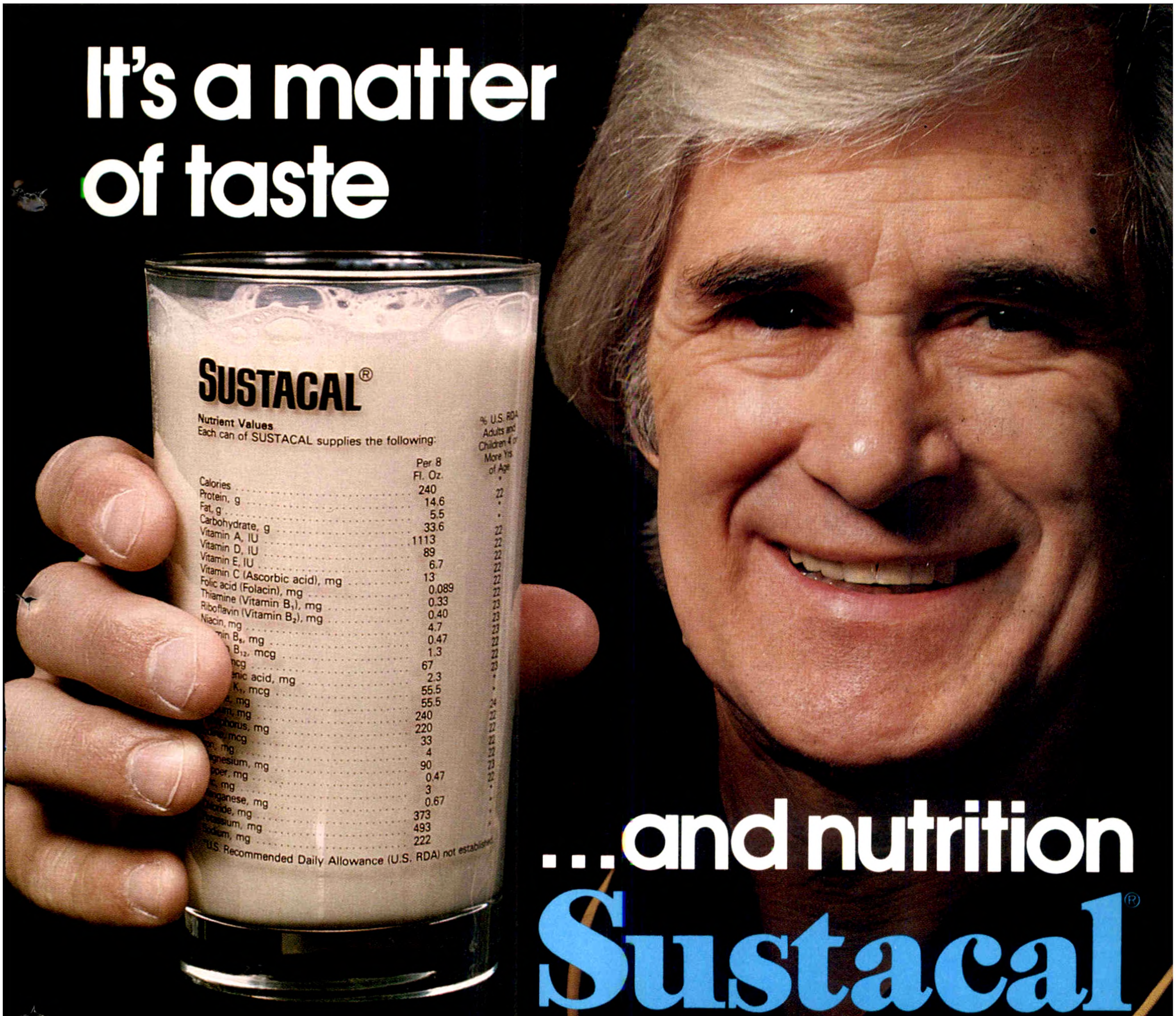
Carpuject® Sterile Cartridge-Needle Units, *1 ml (30 mg)* NDC 0024-1917-02, *1½ ml (45 mg)* NDC 0024-1918-02, *and 2 ml (60 mg)* NDC 0024-1919-02, all in 2 ml cartridge, boxes of 10. Each 1 ml contains pentazocine lactate equivalent to 30 mg base, 1 mg acetone sodium bisulfite, and 2.2 mg sodium chloride, in water for injection.

Multiple-dose vials of 10 ml NDC 0024-1916-01, boxes of 1. Each 1 ml contains pentazocine lactate equivalent to 30 mg base, 2 mg acetone sodium bisulfite, 1.5 mg sodium chloride, and 1 mg methylparaben as preservative, in water for injection.

Winthrop

90 PARK AVENUE
NEW YORK, N.Y. 10016

It's a matter of taste



...and nutrition

Sustacal®

Great tasting nutritional support in a small, easily-consumed serving.

When surgery, therapy or disease reduces your patients' appetites or increases their needs, they need a nutritional boost. They need Sustacal.

Sustacal is a great-tasting nutritional supplement that helps insure daily nutritional needs are met — without replacing the foods patients are eating.

Sustacal is a delicious way to give your patients well-balanced nutrition in a small, easily-consumed serving . . . a maximum amount of nutrition in a minimum volume.

Sustacal comes in a variety of flavors and forms . . . ready-to-use liquid, pudding, and powder that mixes readily with milk.

So, when your patients need extra nutrition, specify Sustacal.

SUSTACAL
NUTRITIONALLY COMPLETE FOOD

Mead Johnson
NUTRITIONAL DIVISION

©1979 Mead Johnson & Company, Evansville, Indiana 47721

International Symposium on Surgical Infections

October 18-19, 1979

Sponsored by
University of Cincinnati
Graduate Surgical Society
Cincinnati, Ohio

In honor of
William A. Altemeier, M.D.
President, American College of Surgeons,
for his contributions to the field

The program will include didactic presentations on nosocimial surgical infections, anaerobic infections, antibiotics, host defense, infections in specific conditions such as trauma, cancer, burns, G.I. surgery, female genital surgery, bone and joint surgery and septic shock, and infections in specific areas such as the lung and urinary tract. There will be an internationally acclaimed faculty including experts for the U.S., Switzerland, Canada, Sweden, England and Italy.

This program is designated as an AMA Category I offering (13¼ hours). The tuition is $175 before September 1, 1979; $200 after September 1, 1979. A detailed program brochure can be obtained from:

Office of CONMED
University of Cincinnati
College of Medicine
231 Bethesda Avenue
Cincinnati, OH 45267
(513) 872-5486

CHANGE OF ADDRESS

Change of Address: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the *Journal.*

Send Change of Address cards to:

ANNALS OF SURGERY
c/o Fulfillment Manager
East Washington Square
Philadelphia, Penna. 19105

KANTREX® CAPSULES
KANAMYCIN SULFATE
NOT FOR SYSTEMIC USE

3506DIRO-08 January 1978

DESCRIPTION
Kanamycin sulfate is a water soluble aminoglycosi
biotic derived from **Streptomyces kanamyceticus.** It is
in oral formulation for topical effect within the gastroi
tract, because it is absorbed only very slightly when admi
orally, and is excreted unchanged in the feces.

ACTIONS
Kanamycin is poorly absorbed from the normal gastro
al tract. The small absorbed fraction is rapidly excre
normal kidney function. The unabsorbed portion of the
eliminated unchanged in the feces.
Most intestinal bacteria are eliminated rapidly follov
administration of kanamycin, with bacterial suppression
ing for 48 to 72 hours.

INDICATIONS
Suppression of intestinal bacteria.—Kanamycin is
when suppression of the normal bacterial flora of the
desirable for short term adjunctive therapy.
Hepatic Coma.—Prolonged administration has been
be effective adjunctive therapy in **Hepatic Coma** by
of the ammonia-forming bacteria in the intestinal tract.
sequent reduction in blood ammonia has resulted in n
improvement.

CONTRAINDICATIONS
This drug is contraindicated in the presence of inte
struction and in individuals with a history of hypersen
the drug.

WARNINGS
Although negligible amounts of kanamycin are
through intact intestinal mucosa (approximately 1 perc
possibility of increased absorption from ulcerated or
areas should be considered. If renal insufficiency deve
ing treatment, the dosage should be reduced or the
discontinued. Urine and blood examinations and au
tests should be given prior to and during extended t
individuals with hepatic and/or renal disease.

USAGE IN PREGNANCY
Safety for use in pregnancy has not been establishe

PRECAUTIONS
Caution should be taken in concurrent use of other
and/or nephrotoxic antimicrobial drugs while kanamyc
ministered orally. These include streptomycin, neomy
myxin B, colistin, viomycin, gentamicin, and cephalorid
The concurrent use of potent diuretics (e.g., ethacr
furosemide, and mannitol, particularly when the diur
given intravenously) should be avoided. They may cau
lative adverse effects of the kanamycin on the kidney
itory nerve.
Prolonged use of oral kanamycin may result in over
nonsusceptible organisms, particularly fungi. If this oc
propriate therapy should be instituted.

ADVERSE REACTIONS
The most common adverse reactions to oral kana
nausea, vomiting, and diarrhea. The "Malabsorption S
characterized by increased fecal fat, decreased serum
and fall in xylose absorption has been reported with
therapy. Nephrotoxicity and ototoxicity have been rep
lowing prolonged and high dosage therapy in hepatic c

DOSAGE AND ADMINISTRATION FOR ORAL USE ON
Suppression of Intestinal Bacteria:
1. As an adjunct in therapy of Hepatic Coma for extend
py: 8 to 12 Gm per day in divided doses.
2. As an adjunct to mechanical cleansing of the large
short term therapy: 1 Gm (2 capsules) every hour f
followed by 1 Gm (2 capsules) every 6 hours for
hours.
Duration of therapy within this range depends on
tion of the patient, the type and amount of concurrent
cal cleansing (catharsis and enemas), and the custom
cal routine.

SUPPLY
KANTREX (kanamycin sulfate) Capsules. Kanamyci
equivalent to 500 mg kanamycin per capsule.
NDC 0015-3506—500 mg
For information on package sizes available, refer t
rent price schedule.

REFERENCES
1. Cohn I Jr: Test your knowledge of intestinal antise
Ther (Hosp Ed) 3:1, (Jan) 1978.
2. Rubbo SD, **et al.**: Role of preoperative chemopro
bowel surgery. **Antimicrob Agents Chemother** 649-6
3. LeVeen Harry H, **et al.**: **Am Journ Surg** 131, (Jan) 1
4. Cohn I Jr: Controlling infection in colon surgery,
(Hosp Ed) 3:1, (Jan) 1978.
5. Cohn I Jr: Controlling infection in colon surgery,
(Hosp Ed) 3:1, (Jan) 1978.
6. Cohn I Jr: **Surg Gynecol Obstet** 130:1006, (Jun) 19

BRISTOL®
©1979 BRISTOL LABORATORI
Div. of Bristol-Myers Company
Syracuse, N.Y. 13201

When did you last use a single aminoglycoside for intestinal antisepsis... with confidence?

Among the several aminoglycosides that are typically employed for pre-op bowel sterilization, Kantrex® (kanamycin sulfate) Capsules have been recognized as "the only antibiotic that can reliably be used alone for intestinal antisepsis."[1] Recent investigations have established that Kantrex Capsules are equal in efficacy with any of the various neomycin combinations—and superior with respect to safety and minimal absorption.

"While the coliform flora was suppressed by neomycin, in approximately 70% of treated cases, the frequency of nausea, vomiting, and diarrhea was disturbingly high. Accordingly, we cannot recommend this regimen. On the other hand, the kanamycin regimen was equally efficient in suppressing the bowel flora and was not associated with any toxic side effects."[2]

"Kanamycin was chosen...because it is safer than neomycin and has a broader spectrum."[3]

"Studies with this agent have shown that its control of the bacterial flora is comparable to that of any of the combinations with neomycin."[4]

"Extensive experience has shown it to be a highly satisfactory agent—well tolerated by patients and free of some of the side effects that neomycin is prone to produce."[5]

"...it is almost quantitatively excreted in the stool and blood levels are too low to measure after oral administration."[6]

Kantrex®

KANAMYCIN SULFATE

a known

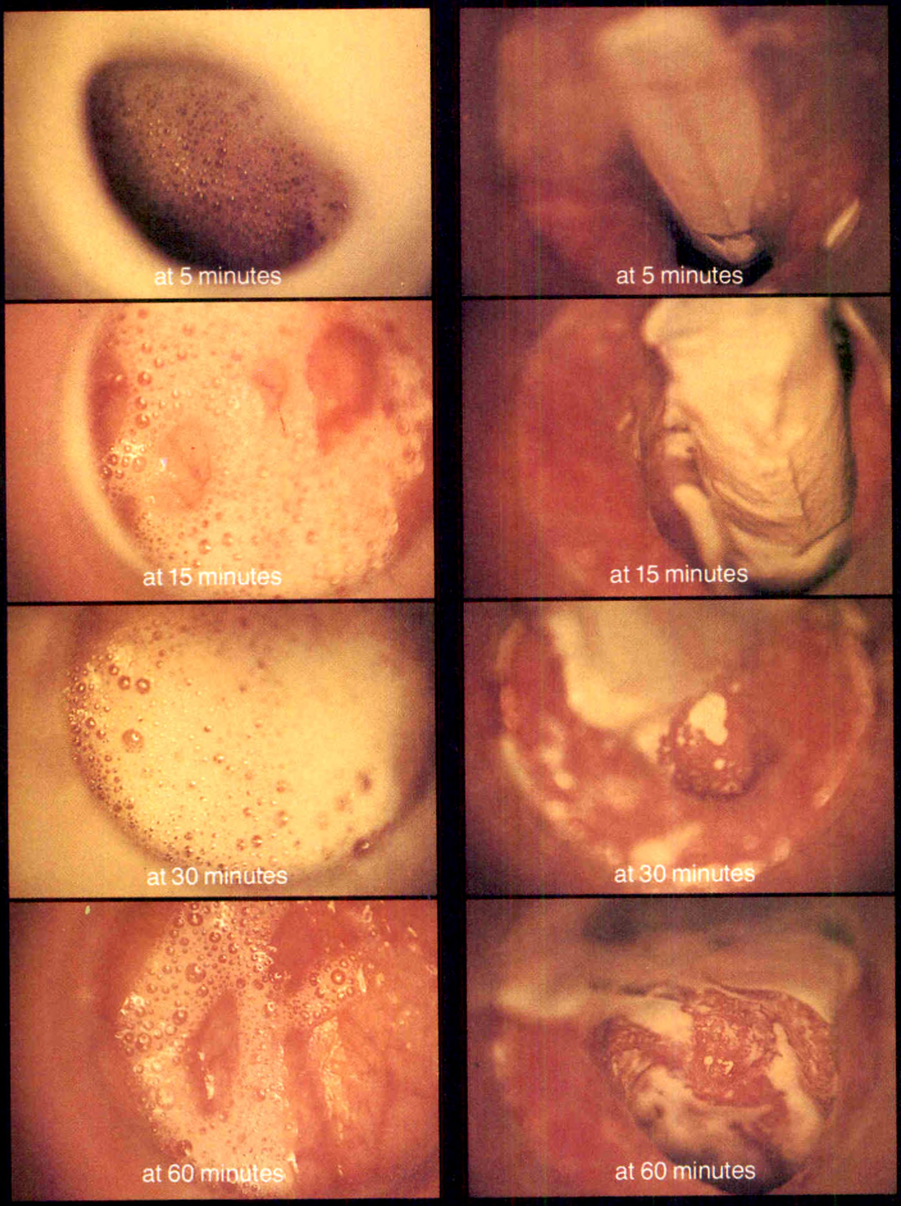
quantity

BRISTOL®

©1979 BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, N.Y. 13201

Through the lenses of a Nikon F2 and a sigmoidoscop

the decisive difference between PROCTOFOAM® and the suppository.


PROCTOFOAM® **The suppository**

The study:

a 36-year-old voluntee
free of rectal pathology
was administered a
traditional hemorrhoi
suppository and
PROCTOFOAM® on
successive days to
determine differences
between the two agent
in speed and extent of
coverage. Both sets of
photographs were take
by a Nikon F2 through
a sigmoidoscope.

Unique photosigmoidoscopic evidence demonstrates the superiority of OCTOFOAM® over the hemorrhoidal suppository in both speed and extent of coverage.

Vithin 5 minutes, PROCTOFOAM® has coated the nucosa of the rectal ampulla while the suppository emains virtually intact.

At 10, 15, and 30 minutes, while the suppository is till in the slow process of melting and giving limited coverage, PROCTOFOAM continues to provide a hick coating on the mucosal surface.

At the end of a full hour, the suppository has finally nelted; coverage is extremely uneven, while PROCTOFOAM continues to provide even coverage.

Jpon application, PROCTOFOAM fills the anal avity, spreading evenly into rectal crypts, folds, papillae and hemorrhoidal sites. And because PROCTOFOAM is mucoadhesive, medication is kept n prolonged contact with tender irritated membranes o bring prompt, sustained and effective relief from tching and pain without leaking or staining.

PROCTOFOAM is available in two formulations: PROCTOFOAM®-HC for temporary relief of acute, nflammatory anorectal disorders and for postoperative pain. PROCTOFOAM-HC provides faster wound nealing[1-4] (2½ to 3 weeks instead of 3½ to 4 weeks);[4] ess scar formation;[1-3] less edema, inflammation, tching, pain and tenesmus.[1, 3-5] Non-steroid PROCTOFOAM® for maintenance therapy when the nflammatory phase has been brought under control.

Both PROCTOFOAM and PROCTOFOAM-HC come with an easy-to-use, measured-dose applicator hat assures proper placement of the medication.

PROCTOFOAM. For faster and more complete overage than the hemorrhoidal suppository.

PROCTOFOAM®-HC
(hydrocortisone acetate 1%)

Before prescribing, see complete product information of which the following is a brief summary.

Contraindications: Topical steroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

Precautions: If irritation develops, the product should be discontinued and appropriate therapy instituted.
In the presence of an infection, the use of appropriate antifungal or antibacterial agents should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.
If extensive areas are treated or if the occlusive technique is used, the possibility exists of increased systemic absorption of the corticosteroid and suitable precautions should be taken particularly in children and infants.
Although topical steroids have not been reported to have an adverse effect on human pregnancy, the safety of their use in pregnant women has not absolutely been established. In laboratory animals, increases in incidence of fetal abnormalities have been associated with exposure of gestating females to topical corticosteroids, in some cases at rather low dosage levels. Therefore, drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.
This product is not for ophthalmic use.

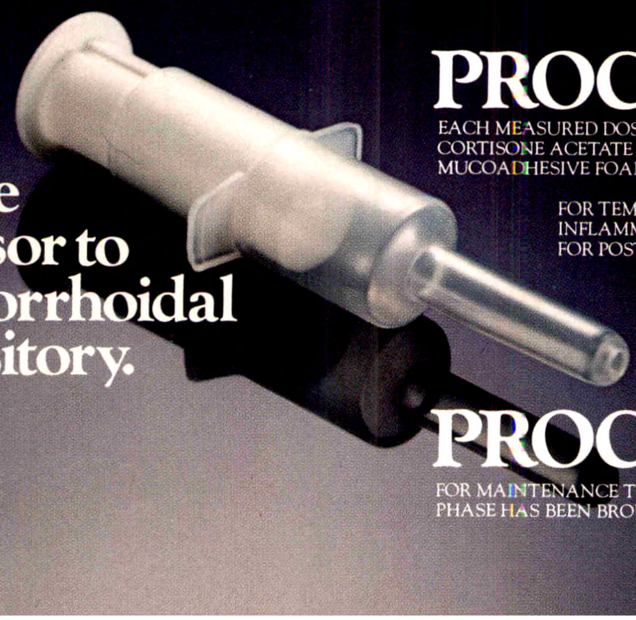
Adverse Reactions: The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

Dosage and Administration: Apply to affected areas 3 or 4 times daily. Use the applicator supplied for rectal application. For perianal use, transfer a small quantity to a tissue and rub in gently.

How Supplied: In aerosol container of 10 gm., with special rectal applicator. The aerosol delivers approximately 24 applications.

References: 1. Bernstein, I.: *Surg. Dig. 4*:23, Jan. 1969. **2.** Sladek, W.R.: Scientific Exhibit, 69th Annual Meeting of American Proctologic Society, April 1970. **3.** Sladek, W.R.: *Am. J. Clin. Res. 1*:33, Jan.-Feb. 1970. **4.** Miller, H.: *Am. J. Proctol. 18*:59, Feb. 1967. **5.** Lieberman, W.: *Am. J. Proctol. 20*:134, April 1969.

Reed & Carnrick/Kenilworth, New Jersey 07033



The uccessor to e hemorrhoidal uppository.

PROCTOFOAM®-HC

EACH MEASURED DOSE (APPROX. 6.5 ML.) DELIVERS HYDROCORTISONE ACETATE 1%, IN A WATER-SOLUBLE, MUCOADHESIVE FOAM BASE.

FOR TEMPORARY RELIEF OF ACUTE INFLAMMATORY ANORECTAL DISORDERS AND FOR POSTOPERATIVE PAIN.

AND **non-steroid**

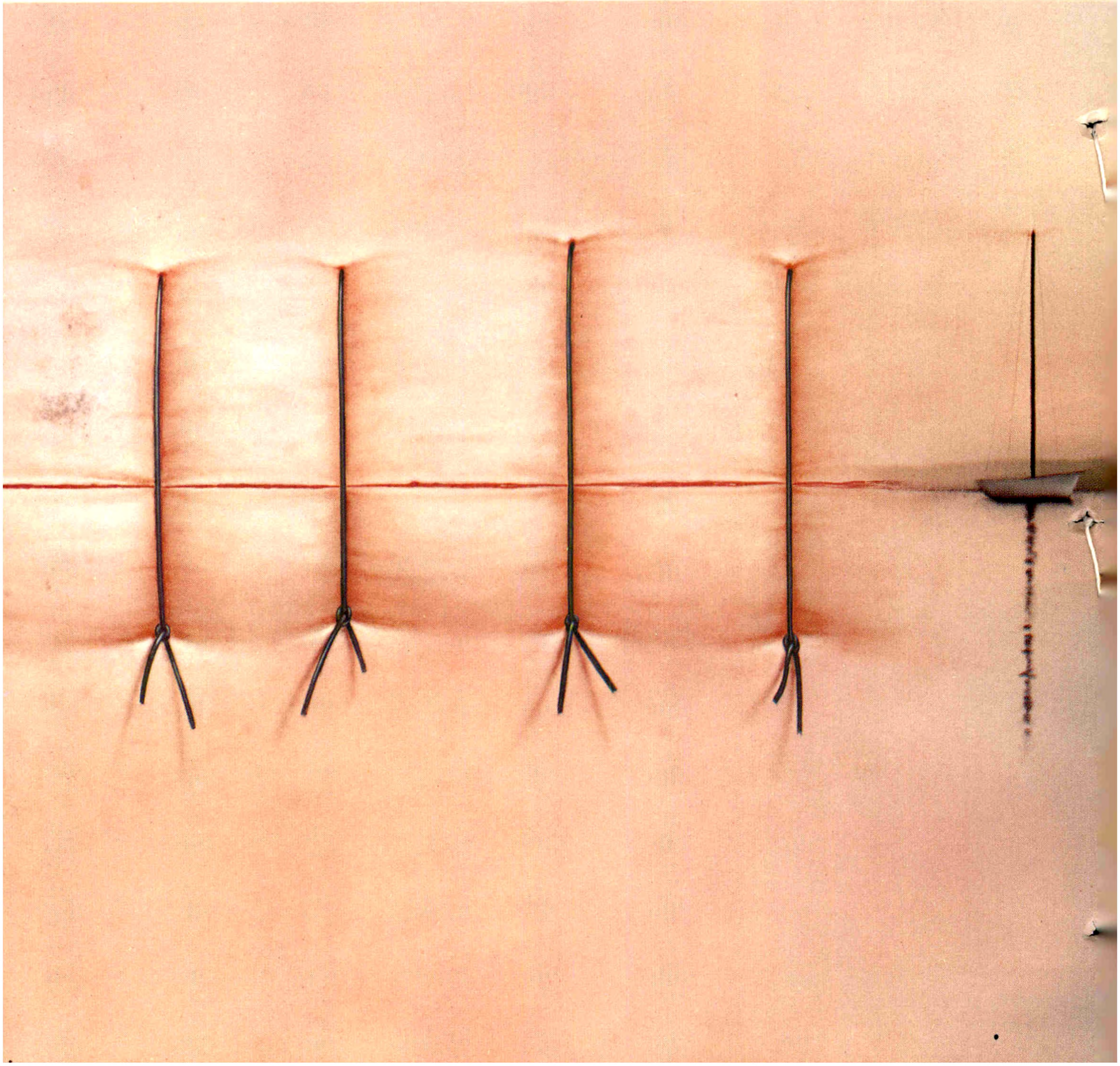
PROCTOFOAM®

FOR MAINTENANCE THERAPY WHEN THE INFLAMMATORY PHASE HAS BEEN BROUGHT UNDER CONTROL.

"...it has long been recognized that anxiety, tension, agitation, and apprehension are all capable of increasing pain perception..."

Halpern L M: Anxiety and pain in postoperative patients. Hospital Practice *(special report), January 1977, pp 31-33.*

Following surgery... the perception of pain diminished by Calm



Vistaril® I.M.
(hydroxyzine HCl)

—reduces the anxiety component of pain
—permits reduction in narcotic dosage
—controls emesis

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.

© 1977, Pfizer Inc.

Vistaril® I.M.

(hydroxyzine HCl)

100 mg/2 ml—50 mg/ml and
25 mg/ml Vials and Isojects®

**preoperatively
and
postoperatively**

- **allays presurgical anxiety... allays the anxiety that may heighten the perception of postoperative pain**
- **may enhance the effects of analgesics and reduce narcotic requirements**
- **controls postoperative emesis**
- **vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)**

BRIEF SUMMARY

VISTARIL® (hydroxyzine hydrochloride)
Intramuscular Solution/For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution is for intramuscular use only and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Since adequate data are not available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscles of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid inadvertent intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended.

Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg/ml–10 ml vials; 50 mg/ml–2 ml and 10 ml vials; Isoject®, 25 mg/ml and 50 mg/ml–1 ml fill; 100 mg/2 ml–2 ml fill.

Military Depot: NSN 6505-00-052-1367 (50 mg/ml, 10 ml vials)

VA Depot: NSN 6505-00-052-1367B (50 mg/ml, 10 ml vials)

More detailed professional information available on request.

Pfizer
LABORATORIES DIVISION
PFIZER INC

ATLAS OF APPLIED VASCULAR SURGERY

■

By KIYOSHI INOKUCHI, M.D.,
and AKIRA KUSABA, M.D.

Here is a unique and timely atlas text describing the wide variety of diseases and lesions that have been successfully treated through vascular anastomoses performed with a new stapling instrument originated and perfected by Dr. Inokuchi.

The extensive experiences of the authors with vessel suturing equipment have extended the use of these instruments beyond the repair and reconstruction of vessels, to other areas of surgery. For example, use of the Inokuchi stapling instrument has made possible the free transplantation of intestine as a reconstruction of the cervical esophagus.

A highlight of the book is a discussion of the many problems and difficulties which arise in portacaval shunt for portal hypertension. The authors have realized success in this operation and describe a new technique—left gastric venous-caval shunt.

This highly descriptive book contains details on the design of the Inokuchi vascular stapler and step-by-step instructions on its use and applications. Many of the operations performed utilizing the device are discussed, describing the techniques used and giving case histories.

198 pages / 301 illustrations, including 68 photographs.
11 in color / 21 Tables / 1975 / $57.00.

Lippincott

J. B. Lippincott Company
East Washington Square • Phila., Pa. 19105

Please send me:

☐ ATLAS OF APPLIED VASCULAR SURGERY $57.00

Name ________________

Address ________________

City ________ State ________ Zip ________

☐ Payment enclosed Save postage & handling ☐ Charge and bill me Plus postage & handling

Also available at your medical bookstore AS 8/79

Role of Arteriography in Rectal Hemorrhage Due to Arteriovenous Malformations and Diverticulosis

E. ARMISTEAD TALMAN, M.D.,* DIRK S. DIXON, M.D.,† FABIO E. GUTIERREZ, M.D.‡

From the Departments of Surgery, Radiology and Pathology, Johnston-Willis and Chippenham Hospitals, Richmond, Virginia

Nine patients with arteriographic right colon arteriovenous malformations (AVM's) are reviewed. Even though five of the eight surviving patients had diverticulosis in remaining colon, right colectomy with removal of the AVM effectively controlled bleeding in seven of the eight patients in follow-up intervals of 14–66 months. Such results suggest that right colon AVM, rather than diverticulosis, may be the more common cause of chronic recurrent lower intestinal hemorrhage in the elderly. Rebleeding occurred in one patient and has heretofore been reported in seven cases. However, since AVM bleeding is rarely life-threatening, right colectomy for chronic recurrent rectal bleeding is justifiable as the initial operative procedure for an AVM, even in the presence of left colon or sigmoid diverticulosis. In the same five year period, 1973–1977, four additional patients with massive hemorrhage, characteristic of diverticulosis, had emergency arteriography with demonstration of a localized site of diverticular bleeding that was controllable by partial colon resection. Consequently, segmental resection of the colon, utilizing selective arteriography, has thus far eliminated bleeding in eight of nine patients with diverticulosis. The judicious use of arteriography in patients with diverticulosis and rectal bleeding substantially reduces the requirement for subtotal colectomy and ileoproctostomy.

RECENT REPORTS of right colon arteriovenous malformations (AVM's) as the source of undiagnosed rectal hemorrhage accentuate the question of the proper role of arteriography. At the same time positive arteriographic findings raise the dilemma of appropriate surgical treatment of such AVM's in patients with concomitant diverticulosis.

This report reviews the data on 13 patients in whom arteriography demonstrated either a right colon AVM or a bleeding diverticulum. The characteristic patterns of bleeding in each entity are analyzed, especially with reference to the justification and timing of arteriography. Suggested surgical management is presented for those patients who may have an AVM or diverticulosis or both lesions simultaneously.

Methods

Since 1973 the surgical policy at our two hospitals has been to try to perform preoperative arteriography in all patients with obscure rectal bleeding who meet clinical criteria for surgical intervention. The approach of our radiologists has been to perform arteriography only after a surgeon has seen the patient, has determined that the patient is a potential operative candidate and agrees that arteriography is indicated.

Two groups of patients with melena were studied by arteriography: 1) patients with recurrent obscure rectal bleeding, and 2) patients with acute massive bleeding requiring emergency surgery. Patients with recurrent obscure rectal bleeding underwent arteriography only if they required at least two hospitalizations and repeated transfusions. Patients with initial episodes of self-limited bleeding were not studied. Patients with massive rectal bleeding underwent emergency arteriography on the basis of imminent surgery for persistent hemorrhage.

The diagnosis of upper gastrointestinal bleeding was by nasogastric suction, fiberoptic endoscopy and barium studies, but not routinely by arteriography. In each case herein reported, gastric aspiration was negative for blood. In the patients with chronic bleeding, proctoscopy and barium studies of the upper and lower bowel were normal except for diverticulosis as stipulated.

Arteriography was performed by the modified Seldinger[45] technique through the femoral artery. Studies in the chronic bleeders were done electively, usually several days after admission when bleeding was sometimes still present but not vigorous. Selective cathe-

---

* Assistant Clinical Professor of Surgery, Medical College of Virginia, Virginia Commonwealth University.

† Radiology Associate, Johnston-Willis and Chippenham Hospitals.

‡ Clinical Instructor in Pathology, Medical College of Virginia, Virginia Commonwealth University.

Reprint requests: E. Armistead Talman, M.D., Johnston-Willis Hospital, 2908 Kensington Avenue, Richmond, Virginia 23221.

Submitted for publication: January 17, 1979.

0003-4932/79/0800/0203 $01.05 © J. B. Lippincott Company

terization was performed of the superior mesenteric, inferior mesenteric and celiac arteries in that order. Film magnification and air insufflation of the colon were not used routinely. No attempts were made at intra-arterial control of bleeding by use of vasoconstricting substances or embolism.

After positive arteriographic study, patients underwent appropriate surgical resections, and pathology confirmed the diagnosis in each instance. Within the five year interval, 1973–1977, only two patients with undiagnosed rectal bleeding underwent exploration without the benefit of positive preoperative arteriograms. One patient had a technically unsatisfactory arteriogram because of celiac and superior mesenteric artery stenosis, and surgery eventually revealed a chronic bleeding gastric ulcer even though gastric aspiration had been negative. The second patient, a 71-year-old man, underwent a successful emergency left colectomy with temporary transverse colostomy for diverticulosis bleeding that was considered too life-threatening to justify delay for arteriography. The right colon was free of diverticula and was later anastomosed to the rectum. The patient has not rebled in the succeeding 33 months.

Results

Thirteen patients with undiagnosed rectal hemorrhage were discovered by arteriography to have either a right colon AVM or extravasation from an actively bleeding diverticulum in the five year interval, 1973–1977. Other pathology causing rectal hemorrhage and demonstrated arteriographically during this interval included a leiomyoma of the jejunum, a leiomyosarcoma of the ileum, a Meckel's diverticulum, a hypersensitivity vasculitis of the cecum, a large uremic cecal ulcer and an unsuspected duodenal ulcer.

Right colon AVM's were present pathologically in nine patients (Tables 1 and 2). All of these patients had a history of repeated hospital admissions and transfusions for unexplained bleeding. None had undergone prior surgical exploration to determine the source. All had intermittent self-limited episodes of gross rectal bleeding, variably dark or maroon, but usually bright red. Most were bleeding significantly on admission with multiple grossly bloody bowel movements and anemia (Table 1). However, in each instance the rectal bleeding diminished spontaneously, permitting complete gastrointestinal evaluation including arteriography. All barium contrast studies were negative except for diverticulosis as specified in Table 2. No patient had any associated angiomatous abnormalities of the skin or other viscera. All nine had positive arteriograms demonstrating at least one AVM in the right colon (Figs. 1–3). All underwent bowel preparation and elective right colectomy. None required emergency surgery.

The first patient underwent right colectomy in 1973, and initial pathology reported a lymphangioma because only dilated submucosal channels were visualized. However, subsequent review confirmed that these were vascular channels consistent with an AVM. This lady who had bled on numerous occasions in the preceding three years has not rebled to the present time.

Patient 5, a 67-year-old man, had colonoscopic examination prior to arteriography. Even though multiple previous barium enemas were negative, colonoscopy revealed two unsuspected sizeable polyps of the sigmoid colon and a telangiectatic AVM was visualized in the hepatic flexure. The latter was subsequently confirmed by arteriography and two other AVM's were identified in the cecum. The polyps were removed and a right hemicolectomy was performed. Pathologically the hepatic flexure AVM appeared to be the source of the hemorrhage; and there has been no further bleeding in the follow-up interval of 29 months.

Five of the nine cases with arteriographic right colon AVM's had diverticulosis elsewhere on barium enema (Table 2). Four of them have thus far been treated successfully by right colectomy alone. In each instance the pathologist identified a right colon AVM before a final decision was made by the surgeon to leave residual colon with diverticulosis. In the two patients with diffuse diverticulosis, there was no suggestion of any bleeding diverticulum in the right colon specimens.

Patient 3, an 80-year-old woman with sigmoid diverticulosis rebled even though the initial cecal AVM seen arteriographically was verified pathologically after right colon resection. Because of recurrent chronic bleeding and anemia, she returned six months later for elective subtotal colectomy and ileoproctostomy. Neither repeat arteriography nor exhaustive pathological examination determined whether the subsequent bleeding was from sigmoid diverticulosis or from additional AVM's; but the patient has been free of bleeding for the succeeding 30 months.

Within the same five year period four patients with diffuse diverticulosis and copious bleeding required emergency surgery (Table 4). All four patients underwent emergency arteriography. In three of them unequivocal extravasation was demonstrated (Fig. 7), and in the fourth there was suspicious extravasation in the right colon. At operation, in the latter patient a pulsatile arterial bleeder from a diverticulum was visualized through a colotomy in the right colon, and a right colectomy was performed. The other three pa-

TABLE 1. *Clinical Experience With Type I AVM In Nine Patients*

Patient	Age/ Sex	Hospital Admissions	Clinical Presentation of Rectal Bleeding	Timing of Arteriogram	Timing of Surgery	Total Units of Blood
1	65/F	Dec., 1971	melena; Hgb. 8.4			2
		May, 1973	recurrent bright red; Hgb. 7.0	3rd day	8th day	4
						6
2	68/M	Feb., 1975	bright red bleeding; Hgb. 13.5			0
		June, 1975	bright red bleeding; Hgb. 6.8	14th day	16th day	7
						7
3	80/F	July, 1975	anemia—positive stools; Hgb. 7.1			5
		Sept., 1975	purple bleeding; Hgb. 6			5
		Nov., 1975	purple bleeding; Hbg. 8.2	3rd day	11th day	2
						12
		April, 1976	post right colectomy bright red bleeding; Hgb. 9.4			2
		May, 1976	post right colectomy bright red bleeding; Hgb. 6.9	6th day	18th day	7
						21
4	50/F	July, 1975	episodic bloody stools for 6 months; Hgb. 9			0
		Dec., 1975	melena			0
		April, 1976	bright red bleeding; Hgb. 6.6			2
		Aug., 1976	heavy red bleeding; Hgb. 5.7	8th day	11th day	6
						8
5	67/M	March, 1975	intermittent black stools; Hgb. 9.7			0
		Sept., 1975	rectal bleeding; Hgb. 9.0			3
		Oct., 1975	bright red rectal bleeding; Hgb. 8.7			2
		June, 1976	weakness—stools positive; Hgb. 6.1	2nd day		2
		July, 1976	readmitted for surgery; Hgb. 9.6		4th day	2
						9
6	77/M	Dec., 1976	large bloody stool; Hgb. 9.1			2
		Jan., 1977	large bright red stools; Hgb. 8.3	9th day	14th day	2
						4
7	72/M	April, 1975	black stools; Hgb. 8.4			3
		Jan. 10, 1977	bright red bleeding; Hgb. 11.4			0
		Jan. 23, 1977	six large bright red stools; Hgb. 9.6	2nd day	4th day	2
						5
8	71/F	Jan., 1977	black stools; Hgb. 7.3			7
		April, 1977	anemia—stools negative; Hgb. 10			0
		July, 1977	black stools with red spots; Hgb. 8.0	12th day	21st day	3
						10
9	86/F	July, 1977	tarry stools; Hgb. 12.3			0
		(had received	16 units previously on multiple admissions to another hospital)			16
		Oct., 1977	black tarry stools; Hgb. 7.1	4th day	17th day	4
						20

tients, on the basis of arteriography without intraoperative examination of the bowel lumen, had appropriate emergency partial colon resections with end-to-end anastomoses. These patients varied in age from 91 to 37 years; and bleeding was massive with a minimal requirement of six units of blood in 12 hours (Table 4). All four patients had diffuse scattered diverticulosis at the time of surgery. None have rebled during follow-up intervals from two years to 32 months.

Discussion

Margulis[32] first demonstrated an AVM by arteriography in 1960, but not until recent years have AVM's been recognized as the most common cause of otherwise unexplained lower intestinal bleeding in patients with negative proctoscopic and barium studies of the gastrointestinal tract.[1,4,9,37] Several comprehensive reports[1,4,9] emphasize the angiographic characteristics

TABLE 2. *Type 1 AVM. Pathology and Follow-up in Nine Patients After Positive Arteriograms and Right Colectomy*

Patient	Age/ Sex	Pathologic Location	Follow-up Without Bleeding	Comments
1	65/F	cecum	5½ yrs.	"lymphangioma"*
2	68/M	cecum	3½ yrs.	*Diverticulosis of sigmoid*
3	80/F	cecum	rebled	*Diverticulosis of sigmoid*—required subsequent subtotal colectomy for rebleeding.*
4	50/F	cecum	Fatal pulmonary embolus	
5	67/M	2 in cecum 1 in hepatic flexure	29 mos.	2 polyps of sigmoid plus AVM of hepatic flexure on colonoscopy. All 3 AVM's on arteriogram.*
6	77/M	1 in cecum 1 in rt. colon	23 mos.	Both AVM's on arteriogram.
7	72/M	right colon	23 mos.	*Diverticulosis diffuse*
8	71/F	8 in cecum	17 mos.	*Diverticulosis diffuse*
9	86/F	multiple cecum & rt. colon	14 mos.	*Diverticulosis left colon*

* Refer to more detailed comment in the text.

of these AVM lesions. Most of the nine patients in this series showed an early draining vein as seen in Figures 1–3.

In 1976, Moore[37] proposed a classification of AVM's. Type 1 AVM's were solitary practically invisible lesions in the right colon which appeared in patients age 55 or older. These lesions required arteriography for detection. Type 2 AVM's were larger lesions, often grossly visible at laparotomy. They occurred most commonly in the small bowel and usually caused blood loss before age 50. Type 3 AVM's occurred as manifestations of congenital and familial multiple telangiectasias (Rendu-Osler-Weber syndrome).

Prior to this report, there were only 52 well documented case reports[3,7,10,13–16,18,20–25,28,29,33,42,43,46–50] of Type 1 AVM's in patients over age 50 in whom the lesion was diagnosed preoperatively by arteriography and subsequently confirmed pathologically.

As early as 1956, Rutter[44] provided a description of a Type 1 AVM discovered in a surgical specimen.

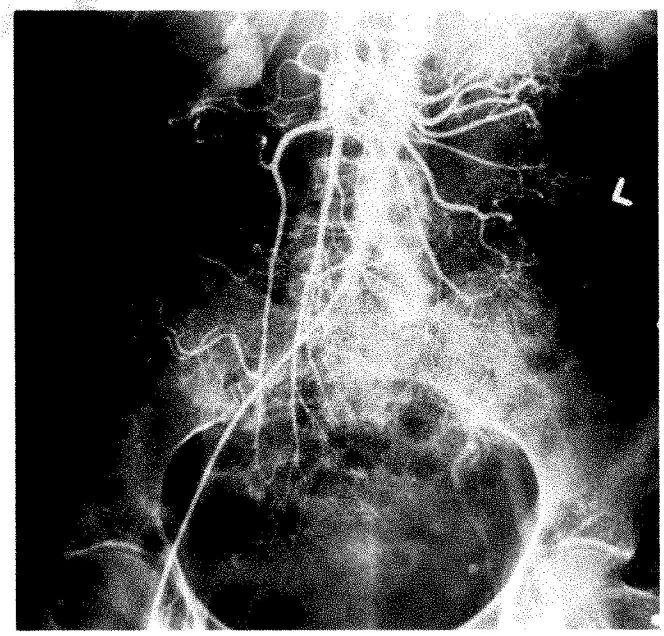


FIG. 1. Early arterial phase of superior mesenteric arteriogram: note the "arterial loop" in the extreme right lower quadrant (Cecum).

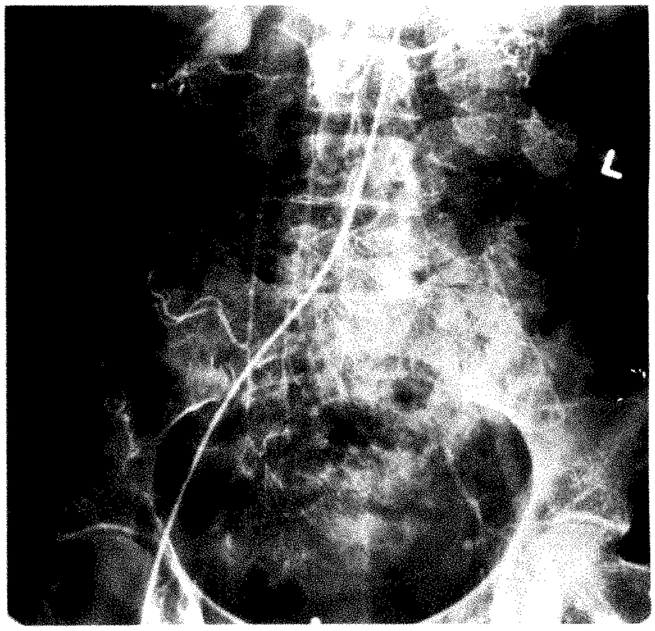


FIG. 2. Late arterial phase: a small early draining vein is seen within the "loop."

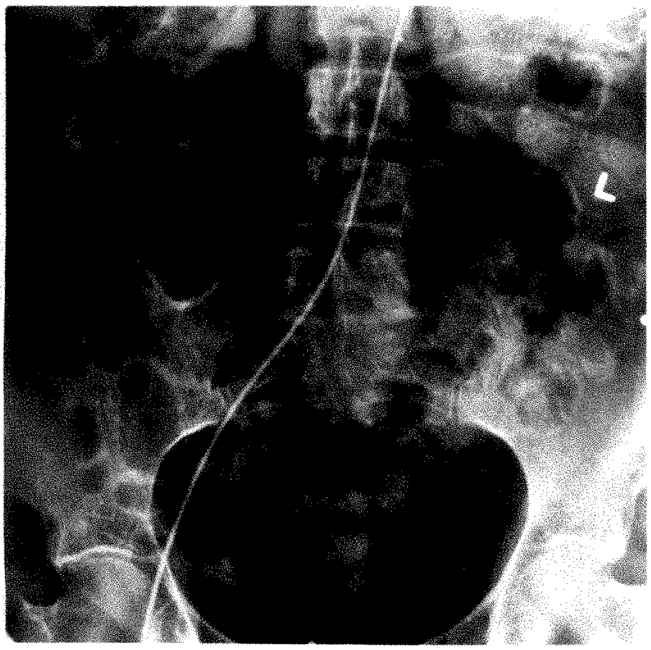


FIG. 3. Venous phase: a large dense ileocolic vein now extends from the small early draining vein seen in Figure 2. Dx.: AVM cecum.

Subsequently, there have been only rare reports of a right colon AVM not demonstrated arteriographically but found in surgical specimens.[27,37] Conversely, Grodsinsky[26] and Whitehouse[53] reported five patients with positive arteriograms in whom no AVM's could be found pathologically.

Obviously, discriminating awareness by both the radiologist and pathologist is essential for successful preoperative and postoperative diagnosis.

With a Type 1 AVM, no gross abnormality is seen on the exterior of the bowel at the time of surgery. When the bowel is opened, the pathology may be apparent only upon close examination of the mucosa. Occasionally there may be a small erosion or ulceration of the overlying mucosal surface. More often one sees only small telangiectasia or petechial or linear hemorrhages (Fig. 4). Sometimes small blood clots are attached. In each instance in Table 2 where the patient had concomitant diverticulosis, an AVM was identified by the pathologist before the final surgical decision to defer subtotal colectomy. Microscopy (Figs. 5 and 6) confirmed these AVM's without resorting to special injection techniques, and serial sections sometimes revealed additional AVM's as well.

Boley[9] presents an hypothesis for the development of these cecal AVM's or ectasias. A series of patients with bleeding and positive arteriograms underwent right colectomy. Specimens were injected with silicone rubber, refrigerated to 4.5° for 24 hours, dehydrated in ethyl alcohol and cleared with methyl salicylate, resulting in a transparent specimen that accentuated the vascular bed. These injected specimens revealed a range of 1–25 AVM's in the cecum and proximal 10 cm of ascending colon. Most patients had one to three AVM's. He proposes that the etiology is chronic partial low grade obstruction of the submucosal veins where they pierce the circular and longitudinal muscles. Submucosal veins become dilated; then the venules, capillaries and arterioles of the mucosa progressively distend, resulting in incompetence of the precapillary sphincter and development of an AV fistula.

TABLE 3. *Type I AVM Cases Previously Reported with Concomitant Diverticulosis. Each Underwent Right Colectomy.*

Author	Age/ Sex	Pathologic Location	Follow-up Without Bleeding	Comments
Showalter[46]	65/F	cecum	3 yr	scattered diverticulosis
Eisenberg[21]	73/F	cecum	18 mo	colonic diverticulosis
Whitehouse[53]	65/M	cecum	7 mo	extensive diverticulosis
Galloway[24]	70/F	cecum	12 mo	sigmoid diverticulosis
Fieber[23]	80/M	cecum		a few diverticula
Bentley[7]	78/M	cecum		sigmoid diverticulosis
Hagihara[27]	54/F	cecum	18 mo	diverticular disease
Randall[42]	79/M	cecum		sigmoid diverticula
Broor[10]	73/M	cecum	9 mo	left colon diverticula

Boley[9] emphasizes that these lesions appear to be ectasias, or dilatations, of normal vascular structures rather than true malformations. He feels that the prevalence of these acquired degenerative lesions in the right colon is attributable to greater tension in the cecal wall. Wangensteen in 1955 applied Laplace's formula to the colon, and emphasized that for any given intraluminal pressure, the tension in the wall is highest in the portion of greatest diameter, namely the cecum. Baum[4] agrees that these ectasias are not congenital, and he speculates that they may be the result of chronic submucosal AV shunting as a manifestation of nonocclusive mesenteric ischemia associated with low cardiac output. It has been suggested that until the etiology is more clearly established, angiodysplasia

TABLE 4. *Diverticulosis. Emergency Arteriograms and Emergency Surgery For Persistent Massive Bleeding*

Age/ Sex	Critical Units of Blood	Localized Site of Extravasation	Operation	Follow-up Without Bleeding
65/M	7 in 12 hr	Right colon	Right colectomy	32 mos.
37/M	10 in 7 hr	Hepatic flexure	Right colectomy	2½ yrs.
75/M	7 in 12 hr	Left transverse colon	Left hemicolectomy	2 yrs.
91/F	6 in 12 hr	Descending colon	Left hemicolectomy	2 yrs.

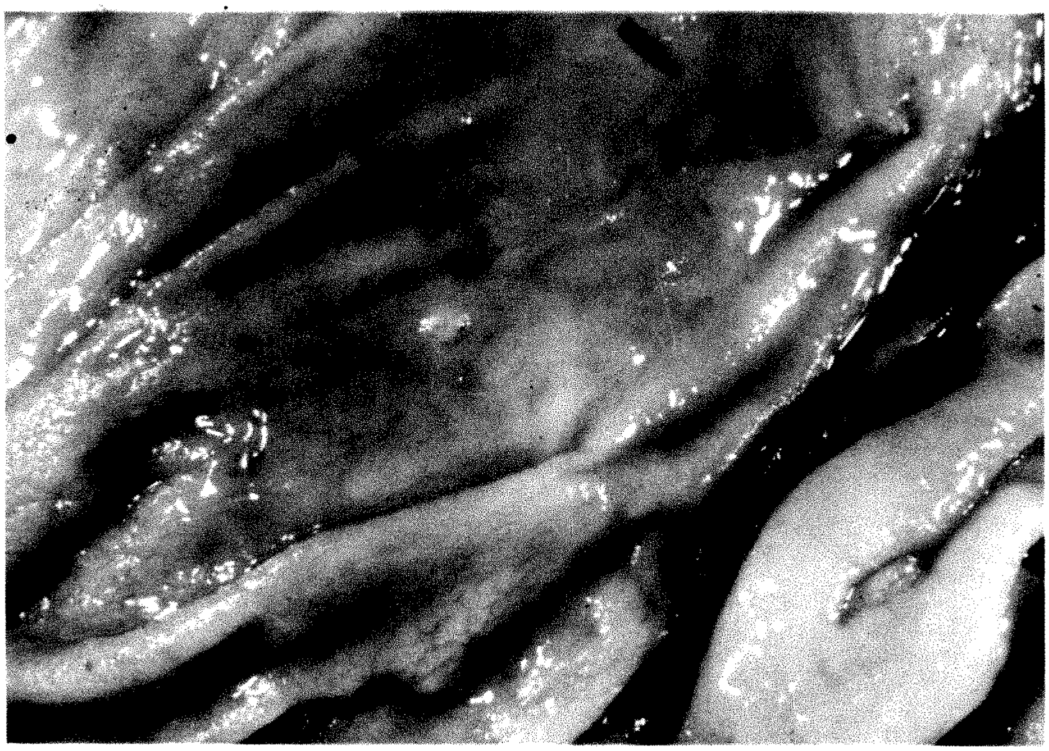


FIG. 4. Small petechial and linear hemorrhages of the colonic mucosa, seen upon careful inspection of the fresh specimens.

may be the preferable designation to avoid the connotation of congenital origin that malformation implies.[13]

These data, of course, raise the question of how many elderly people have incidental AVM's that never bleed? Utilizing the same special injection techniques, Boley[9] examined 15 right colon specimens removed for carcinoma in patients over age 60 that had not bled. Eight of the 15, or over 50% of them, had incidental

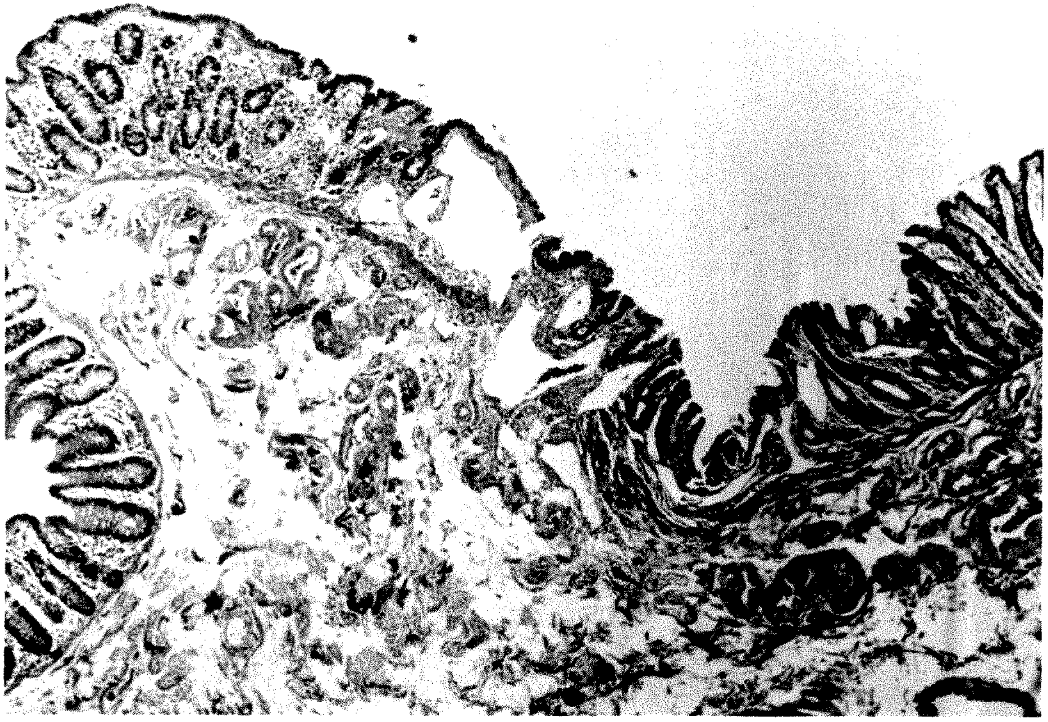


FIG. 5. Abnormal submucosal vessels, some markedly dilated, penetrating through the muscularis mucosa into the mucosa. Note the thin epithelial lining covering a large ectatic vein (H & E, ×40).

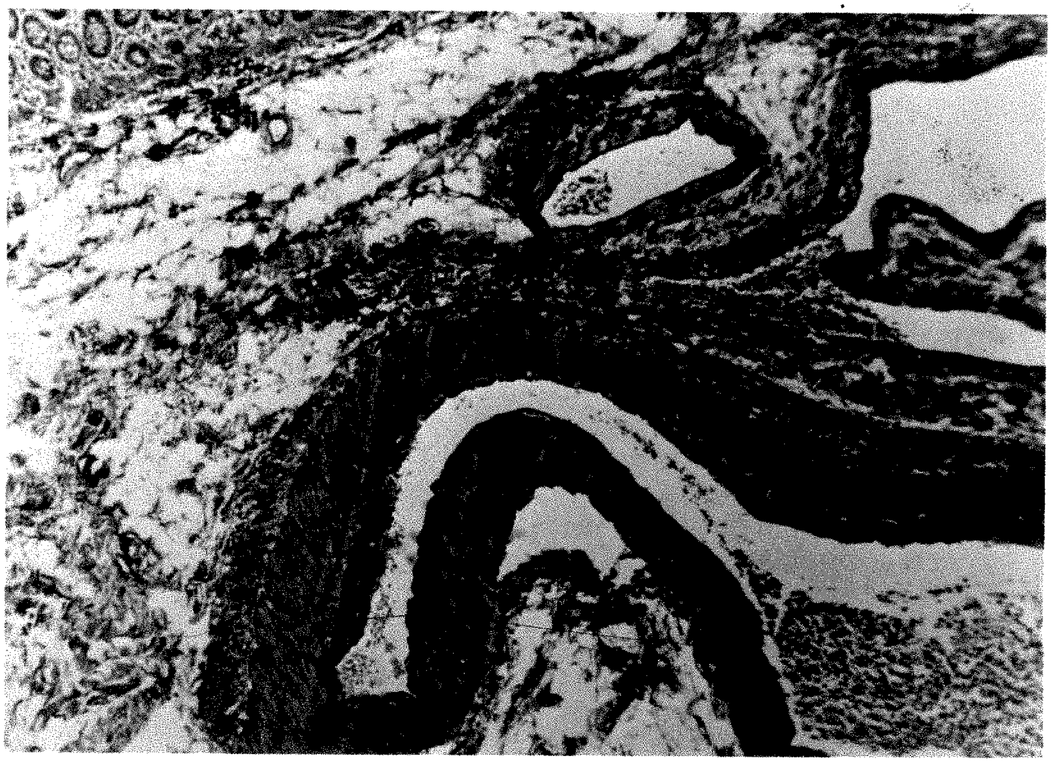


FIG. 6. Compressed submucosal vein and tortuous arteries seen in advanced AVM lesion (VVG, ×100).

AVM's pathologically. On the other hand, Baer[3] in a study of 60 post-mortem and surgically extirpated cecums found no AVM's.

One obvious question is whether there is a clinical difference between AVM's detected arteriographically and the larger number of AVM's seen pathologically by special injection techniques. Perhaps only AVM's large enough to be demonstrable by arteriography are likely to bleed. Likewise, perhaps only AVM's detectable grossly by a knowledgeable pathologist are likely to account for bleeding. Special injection techniques were not necessary in any of our nine cases; and, similarly, almost all of the 52 documented case reports confirmed an AVM without resorting to special injection techniques. Further evidence that these lesions can often be seen grossly comes from multiple reports[8,10,27,49,54] of colonoscopic visualization comparable to the AVM observed in Patient 5.

The association of aortic stenosis and a bleeding cecal AVM has been emphasized by several authors,[3,4-9,24,49] and Patient 9 with an AVM also had aortic stenosis. Baum[4] and Boley[9] suggest that low perfusion may result in ischemic necrosis of the mucosa overlying an acquired ectasia in elderly patients.

The addition of the present series provides a total of 61 arteriographically demonstrated and pathologically confirmed Type 1 AVM's over age 50. Fifty-five patients (91%) have been resectable by some form of right colectomy. The cecum is the most common location, but isolated or simultaneous occurrence in either the distal ileum, ascending colon or hepatic flexure favors standard right hemicolectomy to the middle colic artery. Only six Type 1 AVM cases over age 50 have been reported outside of the right colon or distal ileum.[16,18,21,22,28,37]

Cavett[14] reported arteriographic demonstration of an AVM "of the cecum" that subsequently required resection of additional distal ileum before pathological confirmation of the AVM. This resulted from small bowel overlying the cecum at the time of arteriography. Alfidi[1] suggested intraoperative arteriography to prevent such a misinterpretation, but Crichlow[18] reported mesenteric thrombosis from such an attempt.

There are very few reports of rebleeding following right colectomy for AVM such as occurred in Patient 3. Boley[52] refers to rebleeding in three of 17 patients, and two of these had diverticulosis of the left colon. Welch[52] describes rebleeding in four of 31 AVM patients at follow-up intervals up to 10 years after right colectomy. In two of these cases, repeat arteriograms suggested other AVM's; but the presence of concomitant diverticulosis is not mentioned.

Although emergency subtotal colectomy with ileoproctostomy has had many advocates[19,34,40] for treating patients with massively bleeding diverticulosis, there is now increasing interest in limited colon resection after arteriographic demonstration of the bleeding point.[2,5,12,21,31,35,36] Casarella[12] in 1972 reported 13 such

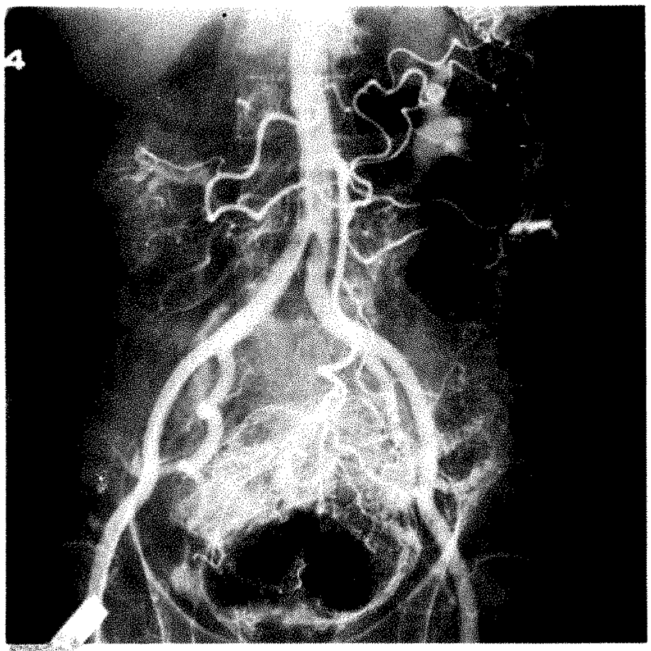


FIG. 7. Inferior Mesenteric Arteriogram: Localized extravasation of contrast into the lumen of the middescending colon demonstrating source of diverticulosis bleeding.

segmental resections for localized bleeding from diverticulosis demonstrated arteriographically. There was one postoperative death from pulmonary embolism. One patient rebled a few weeks later but stopped spontaneously without transfusion. The other 11 did not rebleed in follow-up periods ranging from four months to four years.

Athanasoulis[2] describes similar cessation of bleeding in 12 patients with diverticulosis followed from one to 22 months after segmental resection performed on the basis of arteriographic demonstration of extravasation.

Simultaneous bleeding from two separate diverticula is a rare phenomenon,[11,34,35] and recurrence of bleeding after resection of either a pathologically or arteriographically verified bleeding site seems to be equally unusual.[31] There is only one case report[51] of late diverticulosis rebleeding following partial colectomy when the resected colon has been shown by arteriographic extravasation to be the source of bleeding; and this rebleeding episode occurred two and one half years later.

Nusbaum[39] states that active bleeding sites are demonstrable arteriographically when the rate of hemorrhage is 0.5 cc per minute, or 30 cc per hour. However, Jaffe[30] feels that the rate of bleeding must exceed 6 cc per minute, or 360 cc per hour. He was unable to demonstrate bleeding in laboratory animals at less than 180 cc per hour. All four of the massive diverticulosis bleeders in this series were requiring blood during arteriography and surgery at an average rate of no less than 250 cc per hour (Table 4).

For proper management of the patient, it is important to clarify the significance of the term "massive bleeding." In the recent surgical literature, AVM's are described as the newly recognized cause of "massive"[4,27] and "life-threatening"[9] rectal hemorrhage. This lends considerable confusion to the role of AVM's versus diverticulosis as the source of obscure rectal bleeding in the elderly.

Our experience suggests that one can often clinically differentiate an AVM from diverticulosis by the rate and pattern of bleeding. Each of the four diverticulosis bleeders in Table 4 required at least six units of blood during the 12 critical hours of assessment, emergency arteriography and surgery. Thus, the minimum rate of blood replacement was one-half unit of whole blood (250 cc) per hour. Such a requirement over 12 consecutive hours is indicative of the massive bleeding that accompanies diverticulosis.

On the other hand, none of the nine AVM bleeders required more than three units of blood in any 24 hours, even though each of them received from four to 21 total units over several days and several hospital admissions (Table 2). Such cumulative need for transfusions should not be misconstrued as massive hemorrhage.

Exanguinating hemorrhage from an AVM is most unusual. There is only one AVM case report[23] with mention of emergency surgery. In addition, Beychok[8] reports visualizing a pulsatile stream of arterial blood from an AVM on colonoscopic examination, but this patient also had diverticula in the same area of the pathological specimen.

Truly massive and potentially exanguinating bleeding is still the hallmark of diverticulosis. Impressive documentation comes from Athanasoulis[2] who reports 24 patients in each of whom blood replacement for massive rectal bleeding exceeded five units within the first six hours. All patients had known or subsequently proven colonic diverticular disease, and in all 24 localized extravasation on arteriography demonstrated a diverticulum as the source of bleeding. Many other reports[19,31,34,35,38,40] emphasize this characteristic feature of colonic diverticular hemorrhage.

Consequently, in the presence of diverticulosis and in the absence of significant arteriographic extravasation that might permit limited resection, subtotal colectomy and ileoproctostomy is still the appropriate emergency operation for *acute unremitting* hemorrhage, even if arteriography demonstrates a right colon AVM.

The dilemma of the adequate operation for the patient with *chronic intermittent* bleeding who has sigmoid or diffuse diverticulosis as well as a demonstrated

AVM of the right colon has only recently been appreciated. There have been just nine previous case reports[7,10,21,23,24,27,42,46,53] of right colon Type 1 AVM with concomitant sigmoid or diffuse diverticulosis (Table 3). These nine underwent right colectomy, leaving residual diverticulosis; and no further bleeding occurred in follow-up intervals of seven months to three years. Likewise, five of our nine patients with arteriographic right colon AVM's had concomitant diverticula that were not removed (Table 2). Thus, 14 such cases are herein fully documented.

These data suggest that some patients with diverticulosis who in the past were subjected to elective subtotal colectomy for chronic recurrent rectal bleeding may actually have been bleeding from right colon AVM's. This may also account in part for the preponderance of "diverticulosis" bleeding attributed to the right colon, as well as the frequent failure to demonstrate the bleeding site in resected diverticulosis specimens.[31]

It is of interest that in 1969 Corry and associates[17] reported five cases of "erosions" or superficial ulcers of the cecum coexisting with diverticulosis. Dilated thin walled vessels were noted microscopically but were not then appreciated as AVM's. Even so, the authors advocated initial right colectomy in the face of diverticulosis elsewhere; and, if the resected specimen showed such erosions or superficial ulcers grossly, they felt that surgical resection could be limited to the right colon.

Based on the limited experiences thus far documented (Tables 2 and 3), the proper surgical treatment of a patient with *chronic intermittent* rectal bleeding and both a right colon AVM and diverticulosis elsewhere remains debatable. Perhaps subtotal colectomy as Welch[52] recommends will prove to be preferable. However, right colectomy just for the AVM as advocated by Boley[52] deserves an adequate trial as the initial procedure, in anticipation of less morbidity and mortality. Further follow-up with this approach should provide appropriate answers.

Proposed Management

Diagnostic aspiration of the stomach to exclude an upper gastrointestinal source is essential for any patient admitted with significant rectal bleeding. Other early priorities include a large caliber intravenous line and blood available in the blood bank. Oral intake should initially be withheld and the patient placed at bedrest for close observation to assess the rate of bleeding. These measures seem self-evident but are often overlooked.

If emergency surgery becomes imminent because of persistent massive bleeding, then emergency arteriography is the next procedure of choice. If bleeding is not severe enough to consider emergency surgery, then deliberate delay for complete gastrointestinal radiography seems to be preferable. Subsequent elective arteriographic search for an AVM is justified *only* if the patient has required recurrent hospitalizations and transfusions for similar episodes, or if the bleeding persists even after completion of the routine radiographic evaluation. Such an approach does mean that there may be a rare patient with an AVM who is actually bleeding from diverticulosis and in whom extravasation may be overlooked because of the delayed timing.

Surgeons and radiologists should not become so captivated by the search for an AVM that good clinical judgement is subordinated. Elective surgery for an AVM is more acceptable if the patient has undergone at least two complete gastrointestinal evaluations at separate intervals to exclude other possible sources of bleeding. Welch[52] reports five cases with arteriographic right colon AVM's who were found to have other lesions that were the more likely sources of bleeding. A repeat barium enema within the preceding six months is particularly important because undetected right colon carcinoma remains a frequent cause of obscure rectal bleeding.

To subject all initial rectal bleeders to early arteriography as advocated by Boley[52] would appear to be an unwarranted radiological exercise. The incidence of recurrent bleeding with unresected AVM is still unknown; but the incidence of rebleeding with diverticulosis is only 22%. Almost 80% of the patients in McGuire's[34] series of bleeding attributed to diverticulosis stopped spontaneously and never rebled; and this series must have included many patients who were actually bleeding from AVM's.

A single episode of self-limited, obscure bleeding in an elderly patient usually does not require arteriography. Likewise, recurrent rectal bleeding that does not require blood replacement usually does not warrant surgery and therefore does not justify arteriography. If further investigation is necessary, colonoscopy is probably more reasonable to exclude an occult polyp or carcinoma.

It has sometimes been suggested that empirical or blind right colectomy without the benefit of arteriography may be justifiable in patients with chronic recurrent rectal bleeding, with and without diverticulosis. Certainly, in situations where arteriography is either not available or inadequate, and endoscopy and intestinal x-rays are negative, such surgery may occasionally become necessary. There are two such cases of blind right colectomy with pathological discovery of Type 1 AVM's in the literature.[27,37] However, preoperative demonstration of an AVM certainly makes such resection more tenable; and, consequently, referral for appropriate arteriography is preferable in elective situations.

• Recent experience now substantiates Type 1 AVM as the most common source of otherwise unexplained rectal bleeding. In patients over age 50, 91% of these arteriographically demonstrable lesions have been in the area of the right colon.

However, the clinical significance of AVM's of the right colon is still not adequately appreciated. Even with the addition of our nine patients, there are only 55 well documented right colon cases over age 50 in which there has been preoperative detection of the lesion by arteriography and subsequent pathological confirmation. Duration of follow-up is limited; but for most patients bleeding appears controllable by right colectomy and removal of the AVM.

Arteriography is essential for pre-operative diagnosis of a Type 1 AVM, but extravasation is rarely seen and is not necessary to demonstrate an AVM. Therefore, the patient does not have to be actively bleeding at the time of arteriography.

The proper timing and justification for arteriography in either elective or emergency situations is clinical predetermination that the patient's bleeding is such that surgical control is warranted.

Patients with *chronic recurrent* rectal bleeding and diverticulosis should not be assumed to be bleeding from the diverticulosis until a right colon AVM has been excluded. Since both diverticulosis and Type 1 AVM occur primarily in elderly patients, they probably coexist very frequently. Our data suggest that right colon AVM's may be the more common cause of significant chronic recurrent lower intestinal bleeding in the elderly—rather than diverticulosis. Boley[9] joins us in this speculation.

On the other hand, *acute massive* and unremitting hemorrhage requiring emergency surgery is almost invariably due to diverticulosis. There are few, if any, case reports of this type of hemorrhage from an AVM. Consequently, right colectomy for a demonstrated AVM without significant extravasation cannot be advocated as the emergency operation of choice in the face of massive hemorrhage.

In elderly patients with *chronic recurrent* bleeding, with and without diverticulosis, initial right colectomy for a demonstrated right colon AVM does seem reasonable. This approach is justifiable with the full realization that occasionally subtotal colectomy and ileoproctostomy may subsequently become necessary in a few of the patients with diverticulosis. Reoperation for further chronic bleeding seems more acceptable than subjecting the entire group to initial subtotal colectomy just because they have diverticulosis. Drapanas[19] reported an 11% mortality in 35 patients with subtotal colectomy for bleeding diverticulosis. Ottinger[41] recently found potentially disabling stool frequency in 16% of 43 patients with ileorectal anastomoses.

A similar conservative approach for *acute massive* bleeding from diverticulosis may have more serious repercussions; and in the absence of significant intraluminal extravasation of dye, subtotal colectomy with ileoproctostomy is still the procedure of choice. However, if unequivocal extravasation is demonstrable on emergency arteriography, one can anticipate less morbidity and less mortality by appropriate segmental resection and reanastomosis without removal of the entire colon.

Without the benefit of arteriography, all nine of our patients with diverticulosis and bleeding may well have been considered for subtotal colectomy and ileoproctostomy according to previously popularized criteria. However, utilizing arteriography, only a single subtotal colectomy for nonspecific colon bleeding was necessary in five years at the two hospitals covered in this report.

Consequently, arteriography has a valid role in those cases of undiagnosed lower gastrointestinal hemorrhage, whether chronic and recurrent or acute and copious, in whom either elective or emergency surgery is contemplated. Most particularly this should include patients with known diverticulosis.

References

1. Alfidi, R. J., Esselstyn, O. D., Tavar, R., et al.: Recognition and Angiosurgical Detection of Arteriovenous Malformations of the Bowel. Ann. Surg., 174:573, 1971.
2. Athanasoulis, C. A., Baum, S., Rosch, J., et al.: Mesenteric Arterial Infusions of Vasopressin for Hemorrhage from Colonic Diverticulosis. Am. J. Surg., 129:212, 1975.
3. Baer, J. W. and Ryan, S.: Analysis of Cecal Vasculature in the Search for Vascular Malformations. Am. J. Roentgenol., 126: 394, 1976.
4. Baum, S., Athanasoulis, C. A., Waltman, A. C., et al.: Angiodysplasia of the Right Colon: A Cause of Gastrointestinal Bleeding. Am. J. Roentgenol., 129:789, 1977.
5. Baum, S., Athanasoulis, C. A. and Waltman, A. C.: Angiographic Diagnosis and Control of Large-bowel Bleeding. Dis. Colon. Rectum., 17:447, 1974.
6. Behringer, G. E. and Albright, N. L.: Diverticular Disease of the Colon: A Frequent Cause of Massive Rectal Bleeding. Am. J. Surg., 125:419, 1973.
7. Bentley, P. G.: The Bleeding Caecal Angioma: A Diagnostic Problem. Br. J. Surg., 63:455, 1976.
8. Beychok, I. A.: Precise Diagnosis in Severe Hematochezia. Arch. Surg., 113:634, 1978.
9. Boley, S. J., Sammartano, R., Adams, A., et al.: On the Nature and Etiology of Vascular Ectasias of the Colon. Gastroenterology, 72:650, 1977.
10. Broor, S. L., Parker, H. W., Ganeshappa, K. P., et al.: Vascular Dysplasia of the Right Colon, An Important Cause of Unexplained Gastrointestinal Bleeding. Am. J. Dig. Dis., 23:89, 1978.
11. Casarella, W. J., Galloway, S. J., Taxin, R. N., et al.: "Lower"

Gastrointestinal Tract Hemorrhage: New Concepts Based on Arteriography. Am. J. Roentgenol., 121:357, 1974.

12. Casarella, W. J., Kanter, I. E. and Seaman, W. B.: Right Sided Colonic Diverticula as a Cause of Acute Rectal Hemorrhage. N. Engl. J. Med., 286:450, 1972.
13. Case Records of the Massachusetts General Hospital (Case 36-1974). N. Engl. J. Med., 291:569, 1974.
14. Cavett, C. M., Selby, J. H., Jr., Hamilton, J. L., et al.: Arteriovenous Malformation in Chronic Gastrointestinal Bleeding. Ann. Surg., 185:116, 1977.
15. Clark, R. A. and Rosch, J.: Arteriography in the Diagnosis of Large Bowel Bleeding. Radiology, 94:83, 1970.
16. Cooperman, A. M., Kelly, K. A., Bernatz, P. E., et al.: Arteriovenous Malformation of the Intestine: An Uncommon Cause of Gastrointestinal Bleeding. Arch. Surg., 104:284, 1972.
17. Corry, R. J., Bartlett, M. K. and Cohen, R. B.: Erosions of the cecum, a Cause of Massive Hemorrhage. Am. J. Surg., 119:106, 1970.
18. Crichlow, R. W., Mosenthal, W. T., Spiegel, P. K., et al.: Arteriovenous Malformations of the Bowel: An Obscure Cause of Bleeding. Am. J. Surg., 129:440, 1975.
19. Drapanas, T., Pennington, G., Kappelman, M., et al.: Emergency Subtotal Colectomy: Preferred Approach to Management of Massively Bleeding Diverticular Disease. Ann. Surg., 177:519, 1973.
20. Edie, R. N. and Brennan, J. T.: Colonic Hemorrhage from Arteriovenous Anastomosis: Report of a Case. Arch. Surg., 99: 674, 1969.
21. Eisenberg, H., Laufer, I. and Skillman, J. J.: Arteriographic Diagnosis and Management of Suspected Colonic Diverticular Hemorrhage. Gastroenterology, 64:1091, 1973.
22. Evans, W. E., O'Dorisio, T. M., Molnar, W., et al.: Intra-operative Localization of Intestinal Arteriovenous Malformation. Arch. Surg., 113:410, 1978.
23. Fieber, S. S., Jewel, K. L. and Bodan, R.: Arteriovenous Malformation of the Colon, A Source of Massive Low Intestinal Hemorrhage. J. Med. Soc. N. J., 72:34, 1975.
24. Galloway, S. J., Casarella, W. J., and Shimkin, P. M.: Vascular Malformations of the Right Colon as a Cause of Bleeding in Patients with Aortic Stenosis. Diag. Radiol., 113:11, 1974.
25. Genant, H. K. and Ranninger, K.: Vascular Dysplasias of the Ascending Colon, Report of Two Cases and Review of the Literature. Am. J. Roentgenol. Radium Ther. Nucl. Med., 115:349, 1972.
26. Grodsinsky, C. and Brush, B. E.: Massive Gastrointestinal Hemorrhage Originating from the Cecum. Henry Ford Hosp. Med. J., 19:223, 1971.
27. Hagihara, P. F., Chuang, V. P. and Griffen, W. O.: Arteriovenous Malformations of the Colon. Am. J. Surg., 133:681, 1977.
28. Heald, R. J. and Ray, J. E.: Vascular Malformations of the Intestine: An Important Cause of Obscure Gastrointestinal Hemorrhage. South. Med. J., 67:33, 1974.
29. Hernandez, G. E., Durnin, E. E. and Hagihara, P. F.: Arteriovenous Malformation of the Colon: Case Report. J. Kentucky Med. Assoc., 72:488, 1974.
30. Jaffe, B. F., Youker, J. E. and Margulis, A. R.: Aortographic Localization of Controlled Gastrointestinal Hemorrhage in Dogs. Surgery, 58:984, 1964.
31. Lewis, E. E. and Schnug, G. E.: Importance of Angiography in the Management of Massive Hemorrhage from Colonic Diverticula. Am. J. Surg., 124:573, 1972.
32. Margulis, A. R., Heinbecker, P. and Bernard, H. R.: Operative Mesenteric Arteriography in the Search for the Site of Bleeding in Unexplained Gastrointestinal Hemorrhage. Surgery, 48:534, 1960.
33. Marx, F. W., Gray, R. K., Duncan, A. M., et al.: Angiodysplasia as a Source of Intestinal Bleeding. Am. J. Surg., 134:125, 1977.
34. McGuire, H. H., Jr. and Haynes, B. W., Jr.: Massive Hemorrhage from Diverticulosis of the Colon: Guidelines for Therapy based on Bleeding Patterns Observed in Fifty Cases. Ann. Surg., 175:847, 1972.
35. Meyers, M. A., Volberg, F., Katzen, B., et al.: The Angioarchitecture of Colonic Diverticula. Radiology, 108:249, 1973.
36. Meyers, M. A., Alonso, D. R., Gray, G. F., et al.: Pathogenesis of Bleeding Colonic Diverticulosis. Gastroenterology 71:577, 1976.
37. Moore, J. D., Thompson, N. W., Appelman, H. D., et al.: Arteriovenous Malformations of the Gastrointestinal Tract. Arch. Surg., 111:381, 1976.
38. Noer, R. J., Hamilton, J. E., Williams, D. J., et al.: Rectal Hemorrhage: Moderate and Severe. Ann. Surg., 155:794, 1962.
39. Nusbaum, M., Baum, S., and Blakemore, W. S.: Clinical Experience with the Diagnosis and Management of Gastrointestinal Hemorrhage by Selective Mesenteric Catheterization. Ann. Surg., 170:506, 1969.
40. Olsen, W. R.: Hemorrhage from Diverticular Disease of the Colon. Am. J. Surg., 115:247, 1968.
41. Ottinger, L. W.: Frequency of Bowel Movements after Colectomy with Ileorectal Anastomosis. Arch. Surg., 113:1048, 1978.
42. Randall, P. A.: Chronic Gastrointestinal Bleeding of Unknown Cause. N.Y. State J. Med., Jan.:68, 1977.
43. Reuter, S. R. and Bookstein, J. J.: Angiographic Localization of Gastrointestinal Bleeding. Gastroenterology, 54:876, 1968.
44. Rutter, A. G.: Submucous Telangiectasias of the Colon. Lancet, 2:1077, 1956.
45. Seldinger, S.: Catheter replacement of needle in percutaneous arteriography; new technique. Acta Radiol., 39:368, 1953.
46. Showalter, B., Johnston, D. O. and Wise, R. E.: Arteriovenous Malformation of the Intestine Diagnosed by Arteriography. Lahey Clin. Bull., 19:22, 1970.
47. Siddiqui, A., Ryo, U. Y. and Pinsky, S. M.: Arteriovenous Malformation Simulating Meckel's Diverticulum on ^{99m}Tc-Pertechnetate Abdominal Scintigraphy. Radiology, 122:173, 1977.
48. Singh, A., Shenoy, S., Kaur, A., et al.: Arteriovenous Malformation of the Cecum: Report of Six Cases. Dis. Colon. Rectum. 20:334, 1977.
49. Skibba, R. M., Hartong, W. A., Mantz, F. A., et al.: Angiodysplasia of the Cecum: Colonoscopic Diagnosis. Gastrointestinal Endoscopy, 22:177, 1976.
50. Upson, J. F., Bunnell, I. and Kokkinopoulis, E.: Hemangioma of the Cecum, Diagnosis by Angiography: Report of a Case. JAMA, 217:1104, 1971.
51. Vega, J. M. and Lucas, C. E.: Selective Angiography—Inadequate Guide for Surgery in Bleeding Colonic Diverticula. Arch. Surg., 111:913, 1976.
52. Welch, C. E., Athanasoulis, C. A. and Galdabini, J. J.: Hemorrhage from the Large Bowel with Special Reference to Angiodysplasia and Diverticular Disease. World J. Surg., 2:73, 1978.
53. Whitehouse, C. H.: Solitary Angioblastic Lesions in the Ileocecal Region. Gut, 14:977, 1973.
54. Wolff, W. I., Grossman, M. B. and Shinya, H.: Angiodysplasia of the Colon: Diagnosis and Treatment. Gastroenterology, 72: 329, 1977.

A Long-term Follow-up of Patients Resected for Benign Esophageal Stricture Using the Inkwell Esophagogastrostomy

P. WARA, M. J. ØSTER, P. FUNCH-JENSEN, J. ANDRESEN, P. OTTOSEN

From the Department of Thoracic Surgery, Surgical Gastroenterology and Diagnostic Radiology, University of Århus, Århus Kommunehospital, Denmark

A total of 45 patients have undergone an Inkwell esophagogastrostomy after resection of a benign esophageal stricture. Nineteen patients were available for a long-term follow-up study, showing evidence of gastroesophageal reflux in 16 patients. Due to the high incidence of reflux and subsequent morphologic changes, there was a not negligible late disability. The Inkwell esophagogastrostomy can no longer be recommended in the treatment of an underlying reflux-induced lesion, strictures included.

MOST PAPERS CONCERNING the esophagogastric anastomosis deal with early postoperative complications such as anastomotic leaks and operative mortality.[3,5,18,20,24] Although techniques of the esophagogastric anastomosis have been designed to prevent gastroesophageal reflux,[8,15,18–22,25] very little information is available about late complications induced by gastroesophageal reflux.

By reviewing the literature, symptoms of gastroesophageal reflux are to be expected in 30–50% of the patients, who have undergone an esophagogastrostomy after resection of the lower esophagus including the cardia.[2,21,23] This paper presents the results of a long term follow-up study with special reference to late reflux and morbidity of esophagitis after the "Inkwell esophagogastrostomy," first described by Ottosen and associates in 1959.[20]

Material and Methods

Since 1967 45 patients have undergone an esophagogastrostomy using the Inkwell anastomosis in an intrathoracic position after resection of a distal benign esophageal stricture. (Fig. 1). Preoperatively, malignancy was strongly suspected in 20 patients in spite of negative biopsies. On the other hand, 33 patients had symptomatic gastroesophageal reflux, and 23 patients had a hiatal hernia. All the patients had severe dysphagia. The etiology of the strictures is summarized in Table 1.

The median age was 53 (range 2–70). There were 17 females and 28 males, four of the 45 patients were children. Nineteen patients were available for a follow-up study including a pentagastrin-secretion-test (6 microgram i.m./kg), x-ray studies in order to detect radiologic reflux, stricture formation at the anastomosis and impaired gastric motility expressed by six hours retention. Intraesophageal pH measurements were performed using a modification of a previously reported technique.[6] After placing the pH tube intragastricly the tube was withdrawn and the intrathoracic esophagogastric junction was located manometrically by finding the level at which peristaltic waves after swallowing appeared. The pH tube was then placed 5 cm above this level.

Finally 12 of the 19 patients followed consented to endoscopy in order to study mucosal changes proximal to the esophagogastric anastomosis. In each of these patients the anastomosis had been established between histologically documented undamaged squamouscell-lined esophagus and mucosa of the gastric fundus.

Fourteen patients, who refused to take part in the follow-up study, answered a questionnaire. Together with hospital records this made it possible to compare the symptoms and ability of the patients in the follow-up period (median 3 years, range 6 months–10 years). Of the remaining 12 patients, 7 died from postoperative complications (15%). The cause of death is summarized in Table 2.

Reprint requests: Pål Wara, Department of Surgical Gastroenterology, Århus Kommunehospital, 8000 Århus C, Denmark.

Submitted for publication: December 18, 1978.

0003-4932/79/0800/0214 $00.70 © J. B. Lippincott Company

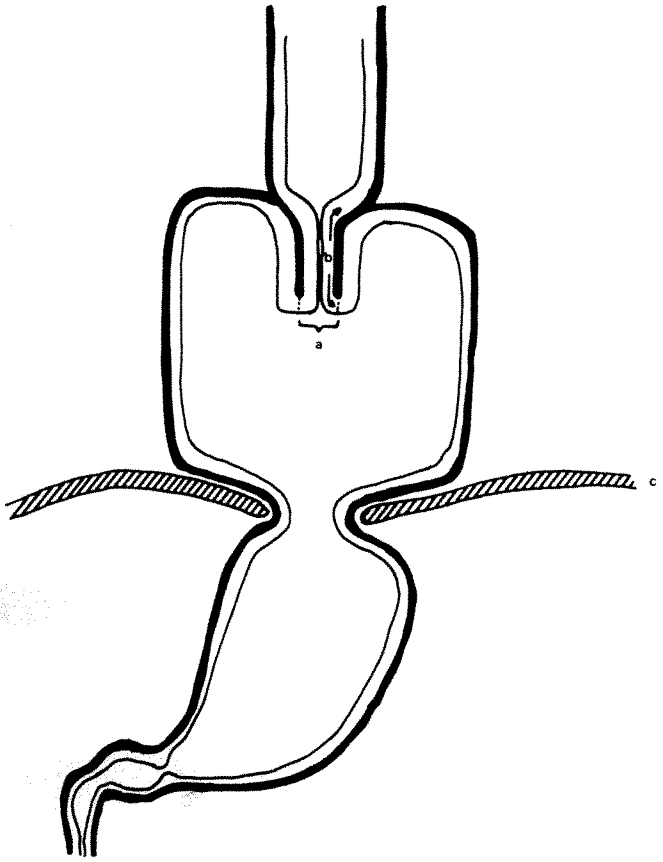


FIG. 1. Diagram of the Inkwell esophagogastrostomy with special reference to a) area of esophageal mucosa exposed to gastric acid; b) area of postoperative specimens; c) diaphragma.

Results

The incidence of gastroesophageal reflux is presented in Table 3. Only 2 out of 19 patients examined did not show evidence of reflux. The invagination figure of the Inkwell anastomosis could be seen clearly in 14 patients. In the remaining three patients studied radiologically, severe regurgitation and retention prevented the visualization of the configuration of the esophagogastric anastomosis. A manometric detectable high pressure zone was not found in any of the patients. The pH reflux test was unsuccessful in four patients due to stricture formation at the anastomosis. Six patients had radiological signs of restricturation. Three of them required intermittent dilatation with bougies (Table 5).

As a part of the esophageal resection all patients were truncal vagotomized, but pyloroplasty was not performed. Ten patients were unable to empty the stomach within six hours. Due to stasis, gastric ulcers occurred in three patients. One patient developed six ulcers, leading to an intractable condition with severe malnutrition.

TABLE 1. *Etiology of the Benign Esophageal Strictures*

Peptic strictures	41
Achalasia	2
Lye stricture	1
Congenital stricture	1
Total	45

Results of the pentagastrin test are presented in Table 4. One half had a peak acid output less than 10 meq/hours. Twelve patients, who were endoscoped, all showed evidence of esophagitis with a hyperemic, vulnerable mucosa. In six patients severe changes with spotted fibrinous covering was observed and in five of these patients the endoscope (diameter 12 mm) could not pass the anastomosis.

Histologically extensive inflammation was confirmed in all patients endoscoped. Proximal to the esophagogastric anastomosis there was a remarkable loss of the original squamous lined epithelium, replaced by gastric epithelium in ten of the 12 patients, containing parietal cells and signs of intestinal metaplasia. In proximal areas still covered by squamous epithelium, papillosis and hyperplasia of the basal cells were observed.

The high incidence of reflux together with the radiological, endoscopical and histological findings, compare favourably with the postoperative symptoms, showing the same tendency in the follow-up group, as in the other patients (Table 5). The symptoms of reflux were most pronounced in the supine position, necessitating almost all patients to sleep in a Fowler's position.

The ability of 30 adult patients in the follow-up period is shown in Table 6. Six patients were able to return to work, while 16 patients were on a pension, seven by disability, nine on social security.

TABLE 2. *Cause of Death in 12 Patients*

	Due to Postoperative Complications		
	Hospital Deaths	After Hospitalization	Died in the Follow-up Period
Cardiopulmonary insufficiency	1		1
Mediastinitis due to			
anastomotic leak	2		
gastric perforation	2		
Aortic bleeding due to			
rupture	1		
gastric perforation		1 (4 months)	
Cachexia due to malignancy (not esophagus)			1
Meningitis			1
Unknown			2
Total	7		5

TABLE 3. *The Incidence of Gastroesophageal Reflux after Inkwell Esophagogastrostomy*

	Reflux Detected	Unsuccessfully Investigated	No Information About Reflux	Reflux Not Detected	Total Investigated
Radiologic reflux	8	2	4	3	17
pH-reflux test	13	4	—	2	19
Radiology and pH-method together	16	1	—	2	19

In addition to the postoperative symptoms and impaired ability, the majority of the patients were unable to gain weight during the follow-up period. Only three patients gained more than 1 kg, and eight of 17 adult patients even lost weight. The average weight change was −6.0 kg (Table 7).

Discussion

In the papers of Ottosen[20] and Lortat-Jacob[15] there are no information about incidence of postoperative reflux. Using a similar technique, entitled "posterior invagination esophagogastrostomy," Okada and associates[18] reported a 20% incidence of postoperative reflux esophagitis, in a later publication[19] 10%. Pearson and Henderson reported a well-defined high-pressure zone in patients without reflux after the Inkwell procedure, but absent in patients with demonstrable radiological reflux.[21] Similar findings were reported by Okada,[18] who added pH recordings to the evalutation.

TABLE 4. *Pentagastrin-secretion-test in 16 out of 19 Patients in the Follow-up Group*

Basal acid output:	median value 0.67 (range 0–4.85) meq/h
Peak acid output:	median value 9.36 (range 0–29.68) meq/h

TABLE 5. *Postoperative Symptoms in 38 Esophagogastrostomized Patients Resected for Benign Strictures*

	Available for Follow-up Study (n = 19)	Not Available for Follow-up Study (n = 19): Information from Questionnaire and Hospital Records (n = 14)	Not Available for Follow-up Study (n = 19): Died in the Follow-up Period, Information from Hospital Records (n = 5)	Total (n = 38)
Symptomatic reflux	14	9	3	26
Dysphagia	7	7	3	17
Bougie treatment	3	1	2	6

Contrary to this, our investigations show a remarkable incidence of postoperative reflux, and in no patient a high pressure zone has been observed. Analyzing the Inkwell procedure, Pearson and Ottosen seemed to use the same technique, both stressing the importance of an invagination of at least 5 cm of esophagus into the gastric fundus.[20,21] We do not agree with Pearson, who indicated a break down of the invagination responsible for the postoperative reflux, but believe epithelial morphologic changes being the causal factor.

In accordance with our study, Hamilton found loss of squamous epithelium, replaced by cardia type mucosa after an average period of two years following esophagogastrostomy and postoperative reflux.[10] These findings suggest a certain latency before developing clinically manifest changes. Other reports confirm the acquired nature of this lesion when esophageal mucosa is exposed to gastric acid.[4,9,16,17]

Thus we believe, that due to the invagination technique, some part of the esophageal mucosa cannot avoid being exposed to gastric acid as illustrated in Figure 1. The initial acid-induced inflammatory changes in the squamous epithelium close to the anastomotic line lead to fibrosis, causing postoperative reflux and further ascending mucosal changes to take place, as the stiff and fibrotic anastomosis acts like an open drain.

We believe, that the reason for the varying results can be explained by the different duration of the follow-up periods. In the series of Pearson and Okada,

TABLE 6. *Ability of 30 Adult Patients*

	Available for Follow-up (n = 18)	Information Not Available from Questionnaire (n = 12)	Total (n = 30)
Returned to work	5	1	6
Disability pension	5	2	7
Social security pension	3	6	9
Capable of light housework	5	3	8

TABLE 7. *Weight Changes in 17 Adult Patients*

Preoperatively:	average 63.4 kg (43–92)
Postoperatively:	average 57.4 kg (29–80)

the patients were almost exclusively operated for malignancy with obviously short observation periods.

There is no doubt that the treatment of benign reflux-induced esophageal lesions should be based on antireflux principles, which are able to stop the progressive ascent of the metaplastic mucosal changes.[17] The Inkwell anastomosis can no longer be regarded as preventing reflux. The curative effect of nonresecting antireflux procedures on peptic esophageal ulceration and even strictures is well documented.[7,11–14,16]

However, when first established, the metaplastic mucosal changes—unlike the inflammatory changes—seem to be irreversible, furthermore with a high incidence of adenocarcinoma occurring in the metaplastic mucosa of the lower esophagus.[1,17] Considering this, every reflux-induced lesion should be followed by regular endoscopical and histologic control.

References

1. Adler, R. H.: The Lower Esophagus Lined by Columnar Epithelium. Its Association with Hiatal Hernia, Ulcer, Stricture and Tumor. J. Thorac. Cardiovasc. Surg., 45:13, 1963.
2. Belsey, R. H. and Skinner, D. B.: Gastroesophageal Reflux and Hiatal Hernia. Boston, Little, Brown & Co. 1972.
3. Borst, H. G., Dragojevic, D., Stegmann, T. and Hetzer, R.: Anastomotic leakage, Stenosis and Reflux after Esophageal Replacement. World J. Surg. 2:861, 1978.
4. Bremner, C. G., Lynch, V. P. and Ellis, F. H.: Barrett's esophagus: Congenital or Acquired? An Experimental Study of Esophageal Mucosal Regeneration in the Dog. Surgery, 68:209, 1970.
5. Chassin, J. L.: Esophagogastrectomy: Data Favouring End-to-Side Anastomosis. Ann. Surg., 188:22, 1978.
6. Csendes, A., Øster, M., Møller, J. T., et al.: Gastroesophageal Reflux in Duodenal Ulcer Patients Before and After Vagotomy. Ann. Surg., 188:804, 1978.
7. DeMeester, T. R., Johnson, L. F. and Kent, A. H.: Evaluation of Current Operations for the Prevention of Gastroesophageal reflux. Ann. Surg., 180:511, 1974.
8. Ellis, H. F. and Hood, R. T.: Experimental Esophagogastrectomy: Relation of Type of Resection to Development of Esophagitis. Surg. Gynecol. Obstet., 98:449, 1954.
9. Halvorsen, J. F. and Semb, B. K. H.: The "Barrett-syndrome" (the Columnar-lined Lower Esophagus): An Acquired Condition Secondary to Reflux Esophagitis. Acta Chir. Scand., 141: 683, 1975.
10. Hamilton, S. R. and Yardley, J. H.: Regeneration of Cardiac Type Mucosa and Acquisition of Barrett-mucosa After Esophago-gastrostomy. Gastroenterology, 72:669, 1977.
11. Herrington, J. L., Wright, R. S., Edwards, W. H. and Sawyers, J. L.: Conservative Surgical Treatment of Reflux Esophagitis and Esophageal Stricture. Ann. Surg., 181:552, 1975.
12. Hill, L. D., Gelfand, M. and Bauermeister, D.: Simplified Management of Reflux Esophagitis with Stricture. Ann. Surg., 172: 638, 1970.
13. Hill, L. D.: Progress in the Surgical Management of Hiatal Hernia. World J. Surgery, 1:425, 1977.
14. Larrain, A., Csendes, A. and Pope, C. E.: Surgical Correction of Reflux. An Effective Therapy for Esophageal Strictures. Gastroenterology, 69:578, 1975.
15. Lortat Jacob, J. L., Maillard, J. N. and Fekete, E.: A Procedure to Prevent Reflux After Esophagogastric Resection: Experience with 17 Patients. Surgery, 50:600, 1961.
16. Naef, A. P. and Savary, M.: Conservative Operations for Peptic Esophagitis with Stenosis in Columnar-lined Lower Esophagus. Ann. Thorac. Surg., 13:543, 1972.
17. Naef, A. P., Savary, M. and Ozzello, L.: Columnar-lined Lower Esophagus: An Acquired Lesion with Malignant Predisposition. J. Thorac. Cardiovasc. Surg., 70:826, 1975.
18. Okada, N., Kunyama, T., Umemoto, H., et al.: Esophageal Surgery: A Procedure for Posterior Invagination Esophagogastrostomy in One-Stage without Positional Change. Ann. Surg., 179:27, 1974.
19. Okada, N., Tagami, Y., Morishita, H., et al.: Reconstruction of the Esophagus by Posterior Invagination Esophagogastrostomy. World J. Surg., 1:361, 1977.
20. Ottosen, P., Behrendt, F. and Søndergaard, T.: Treatment of Carcinoma of the Esophagus and Cardia. Description of a New Operative Technique. Acta Chir. Scand., 117:181, 1959.
21. Pearson, F. G., Henderson, R. D. and Parrish, R. M.: An Operative Technique for the Control of Reflux Following Esophagogastrostomy. J. Thorac. Cardiovasc. Surg., 58.668, 1969.
22. Seta, K., Hatajuku, T., Higuchi, T. and Watanabe, M.: A Method of Valvuloplastic Esophagogastrostomy to Prevent Reflux after Proximal Gastrectomy. World J. Surg., 2:851, 1978.
23. Skinner, D. B. and Booth, D. J.: Assessment of Distal Esophageal Function in Patients with Hiatal Hernia and/or Gastroesophageal Reflux. Ann. Surg., 172:627, 1970.
24. Skinner, D. B.: Esophageal Malignancies. Experience with 110 cases. Surg. Clin. North Am. 56:137, 1976.
25. Watkins, D. H., Prevedel, A. and Harper, F. R.: A Method of Preventing Peptic Esophagitis Following Esophagogastrostomy. J. Thorac. Surg., 28:367, 1954.

The Role of Cardiovascular Hemodynamics and Liver Histology in Evaluating Bleeding Cirrhotic Patients

V. DICARLO, C. STAUDACHER, R. CHIESA, B. ANDREONI, M. CRISTALLO, E. RONCHETTI

Preoperative cardiovascular hemodynamics and percutaneous liver biopsies were used to evaluate the pathophysiologic factors determining the operative prognosis of patients with cirrhotic liver disease and bleeding esophageal varices. These studies confirm the observations of Siegel that the greater the magnitude of the peripheral abnormalities in vascular tone and oxygen consumption the better must be the capability of the ventricular function, if the cirrhotic is to survive emergency or urgent portal decompressive surgery. These studies also show that the cardiovascular hemodynamics are directly correllated with the nature and degree of the abnormalities in the liver biopsy, and that pathologic and physiologic features of this disease which impact on surgical prognosis can be expressed through the easily obtained Survival Index. Bleeding cirrhotic patients with poor quality hemodynamics and poor histologic characteristics should be treated non operatively, since the operative mortality appears greater than that produced by a strategy of medical supportive therapy and delayed surgery if stabilization occurs.

From The Institute of Emergency Surgery, University of Milan, Italy

NO OTHER HEMORRHAGE in the digestive tract poses such delicate therapeutic problems as those which complicate portal hypertension in cirrhotic patients. Hemorrhagic shock is more serious in such patients not only because of the amount of blood lost but also due to the relative insufficiency of physiological compensatory mechanisms and to the hepatic decompensation which often occurs when blood is absorbed from the intestine. In the cirrhotic patients an abnormal hemodynamic situation exists which is capable of definitively conditioning the patients response to stress due to hemorrhage or to necessary decompressive surgery.[2,4,11]

The knowledge of the different types of cardiovascular pathophysiologic responses provides a decisive basis for a more rational medical care, for deciding which patients should or should not be subjected to an emergency operation, for timing of elective surgery and for postoperative management.

Moreover, histological studies of the liver performed during active bleeding have outlined the influence of acute hyaline necrosis on mortality in patients not operated on and on mortality after emergency and elective portacaval shunt.[5-7] These two parameters, cardiovascular hemodynamics and histological examination of the liver, are at present the most valid criteria for prognosis and rational treatment of the cirrhotic patients bleeding from esophageal varices. The purpose of this study was to examine in detail some of the physiologic abnormalities associated with massive hemorrhage and to integrate this information with histological results from percutaneous liver biopsies performed using a posterior approach, in an attempt to evaluate short-term prognosis and a more accurate prediction of postoperative survival. Hemodynamic changes were also correlated with the degree of liver damage.

Materials and Methods

Hemodynamic Measurements

Between June 1975 and December 1977, 66 patients with cirrhosis and portal hypertension, admitted to the Institute of Emergency Surgery of the University of Milan for massive bleeding from esophageal varices, underwent cardiovascular hemodynamics and oxygen consumption evaluation. The patients studied were selected from a larger group admitted to hospital during the same period on the basis of hemorrhage severity.

The source of bleeding was diagnosed by clinical, endoscopic and angiographic examination. Hemodynamic measurements were performed using a subclavian catheter positioned in the right atrium or a

---

Reprint requests: Dr. V. DiCarlo, Instituto Di Chirurgia D'Urgenza, Dell 'Universita Di Milano, Ospedale Policlinico, Via F. Sforza, 33, 20112 Milano, Italy.

Submitted for publication: December 18, 1978.

This investigation was supported in part by Centro Nazionale delle Richerche grant.

0003-4932/79/0800/0218 $00.95 © J. B. Lippincott Company

7 F triple lumen Swan-Ganz catheter floated in the pulmonary artery; a Teflon® catheter was inserted into the femoral artery percutaneously or into a surgically exposed radial artery. Pressures were measured using Bently Trantee transducers and recorded on a MFE poligraph. Cardiac output was measured in fifty patients by the thermal dilution method (Output Computer, Edwards) and in 16 patients by the dye dilution method using indocyanine green and a Waters densitometer. Blood gas was determined using an ABL 1 Radiometer blood gas analyzer, and O_2 content in the arterial and mixed venous blood was measured by Lex O_2 Con (Lexington).

The computations of hemodynamic data were made with a portable computer (HP 97 Hewlett Packard) and using a cardiovascular program developed by Siegel et al.[12] The following parameters were calculated: cardiac index (CI), left ventricular stroke work (SW), total peripheral resistance (TPR), oxygen consumption/square meter (O_2 cons/m^2) and effective O_2 transport (EOT). For a graphic representation of these parameters which provides a physiologic frame of reference to previously studied patient groups including normal and patients in various pathophysiologic states of compensation, we have utilized the four diagrams proposed by the same authors.[12] These plots represent the following functions: Vascular Tone, Effective Oxygen Transport, Relative Peripheral Shunting and Ventricular Function. From the Relative Peripheral Shunting Index and Ventricular Function Index a Survival Index was calculated which has been shown to express the probability of survival for the cirrhotic patient from major hemorrhage or following surgical portal decompression.

TABLE 1. *Histologic Classification of the Liver Lesions*

Group I	normal aspect of the liver (prehepatic portal hypertension)
Group II	structural alterations without active flogosis or degenerative lesions or important necrosis of the liver (inactive cirrhosis, post-necrotic cirrhosis, congenital fibrosis).
Group III	structural alterations with important activity of chronic liver process, but with slight liver tissue lesions (chronic active hepatitis, chronic alcoholic liver disease with fibrotic evolution).
Group IV	structural alterations with important degenerative lesions and parenchyimal necrosis (chronic liver disease with important alcoholic or viral or ischemic reactivation).

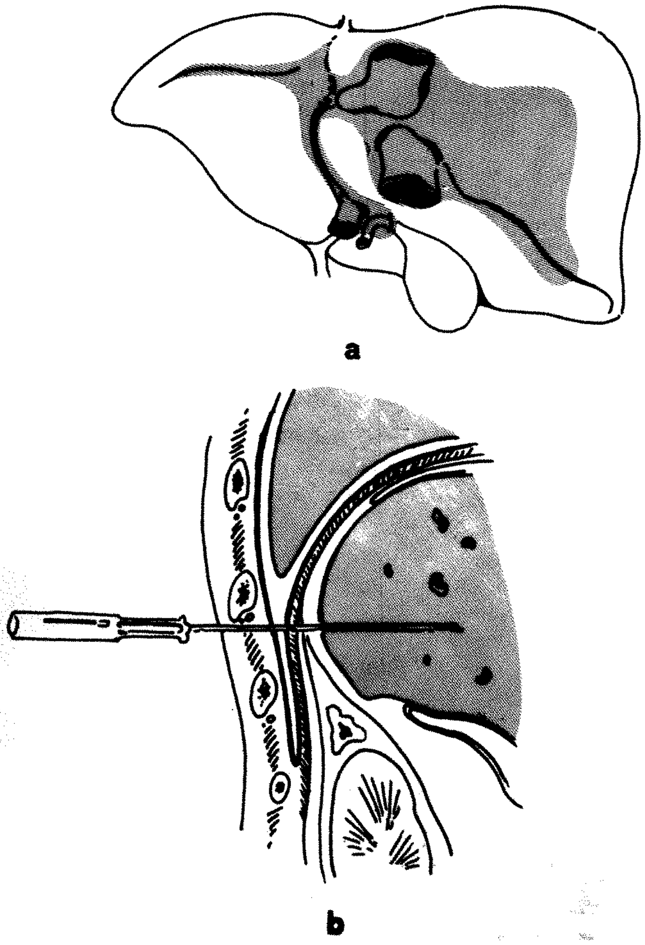


FIG. 1. Extraperitoneal approach for percutaneous needle liver biopsy: a) Posterior view of the liver. The shaded area shows the extraperitoneal insertion of coronaric ligament. b) Sagittal section with the course of the needle during the biopsy. The needle introduced at the level of the superior margin of the eleventh rib, crosses the costal-diaphragmatic sinus, the diaphragm and the right coronaric ligament.

Histological Study

Percutaneous liver biopsy was performed using a posterior approach. Under local anesthesia and with the patient recumbent in a prone position, the needle (Tru-Cut, Travenol) was introduced at the level of the superior margin of the 11th rib about 6–7 cm from the median line. This method offers the advantage of penetrating the liver across the extraperitoneal space through the coronary ligament without the danger of biliary diffusion or hemorrhage (Fig. 1). A previous coagulation study is not required. Histological results are available within 18 hours. Histological findings were classified in four groups (I–IV Table 1). On the basis of the degree of necrosis and of degenerative lesions, group IV was subdivided into two subgroups with *moderate* changes (IV*m*) and *severe* changes (IV*s*) respectively. Between 1975 and 1977, 156 successful liver biopsies were performed on patients with portal hypertension: 93 in actively bleeding patients and 63 in patients studied during a period remote in time from previous episodes of hemorrhage.

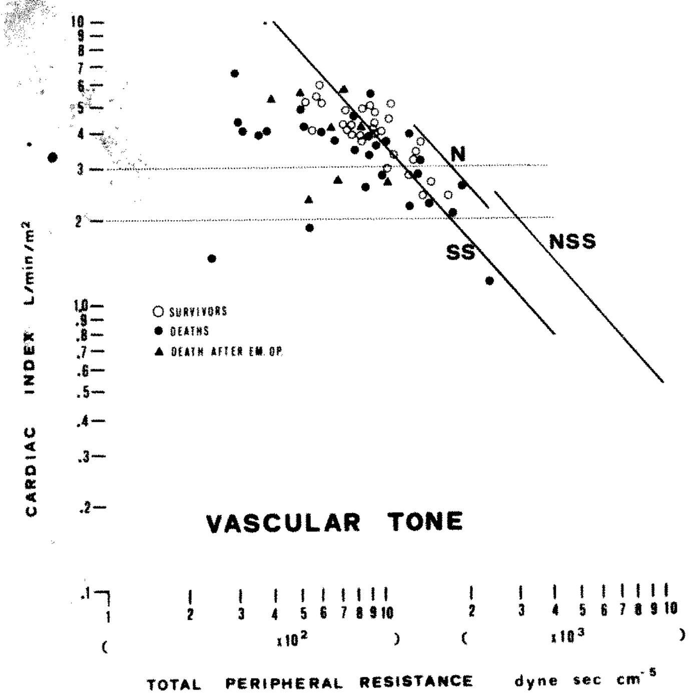


FIG. 2. Vascular tone in bleeding cirrhotic patients. Log-log plot of the cardiac index in liters/min/m² versus the total peripheral resistance in dyne-sec-cm⁻⁵. Points representing our patients are plotted against the Siegel's means for groups of patients in state of septic (SS) and non septic (NSS) and older normal patients (N) who were not in a state of shock and had no known liver disease.[12]

Results

Hemodynamic Findings

Cirrhotic patients with bleeding from esophageal varices show a very different hemodynamic pattern from that observed in patients with bleeding due to other causes. The difference in pattern is more evident 48 hours after hemorrhage when the blood volume is replaced.

We have studied and analyzed the following four functions.[12]

Vascular tone. Vascular tone (Fig. 2) is a means of gaining insight into the degree of net vasoconstriction or vasodilitation of the vascular tree.[11] In this relationship the peripheral vascular resistance is evaluated as a function of flow (cardiac index) to provide a comparison with values obtained from other individuals. In this figure the values from cirrhotic patients were compared to the mean slopes of vascular tone relations previously determined for patients with septic, and non septic shock, and for normals.[11] The use of these lines derived by Siegel[11,12] in this, and the other physiologic figure provides a coordinate system whereby the abnormal physiologic characteristics found in cirrhotic patients can be *compared* to previously studied cirrhotics and other types of serious disorders of physiologic compensation. This is especially important to the understanding and quantification of the cirrhotic abnormalities, since as previously shown, cirrhotic patients with portal hypertension have a decrease in vascular tone equal to or greater than that seen in severe septic shock.[11]

The vascular tone changes in these 66 patients are strikingly similar to those reported by Siegel.[11] However, some important new facts should be ascertained from these data. Hemorrhage produced an important change in vascular tone. After replacement of the blood lost all the patients except 18 became hyperdynamic (CI > 3 l/min/m²), while the peripheral vascular resistance decreased to clearly lower levels than those observed in cirrhotic patients with portal hypertension but no recent hemorrhage.

Vascular tone was lower than normal in all patients (Fig. 2); this abnormality may have prognostic significance. Patients who died are clearly divisible from septic patients. Also, patients who remained hypodynamic or normodynamic after blood volume replacement had a high mortality rate (14 deaths in 18 patients). When peripheral resistance was lower than 550 dyne/sec/cm⁻⁵ no patient survived. Emergency surgery had poor results if patients showed serious abnormality in vascular tone (8 out of 15 died).

Effective oxygen transport. Oxygen consumption/min/m² is a critical determinant of metabolic adequacy in the cirrhotic patient, and cirrhotic patients with portal hypertension and low Effective Oxygen Trans-

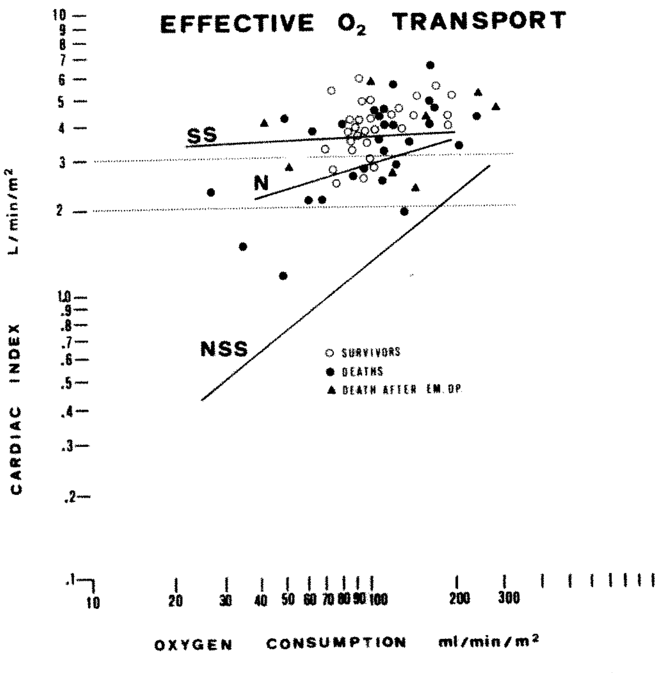


FIG. 3. Effective oxygen transport in bleeding cirrhotic patients. Log-log plot of cardiac index in liters/min/m² versus oxygen consumption in milliliters/min/m².[12]

port (EOT) have been shown to have poorer operative prognosis than those with normal or increased EOT. The nature of this abnormality is similar to that found in sepsis and Figure 3 shows the grid lines relating flow and oxygen consumption developed by Siegel[11] which permit this function to be defined by regions of different flow: O_2 consumption relations. In the present study when oxygen consumption was evaluated as a function of total blood flow (Fig. 3), it was seen that about 80% of our patients had an oxygen extraction abnormality similar to that found by Siegel et al.[11-14] in both hyperdynamic septic or cirrhotic patients. They required a higher peripheral flow at each level of oxygen consumption than that required by patients in other groups. All seven patients who could not maintain an oxygen consumption higher than 70 ml/min/m² died.

Relative peripheral shunting. The relative peripheral shunting function which relates the level of oxygen consumption as a function of the total peripheral resistance is perhaps the most important physiologic relationship expressing the adequacy of peripheral perfusion.[11,12] It is an attempt to demonstrate to what extent the diminished vascular tone is functionally related to the reduced oxygen consumption. Again, the use of the coordinate system developed by Siegel using the different physiologic limits seen in septic and non septic shock states, and applied by him to the study of patients with cirrhosis and portal hypertension[11,12] is used to delineate the physiologic region of greatest risk. The data in the present physiologic studies of our Italian patients confirm the previous American studies.

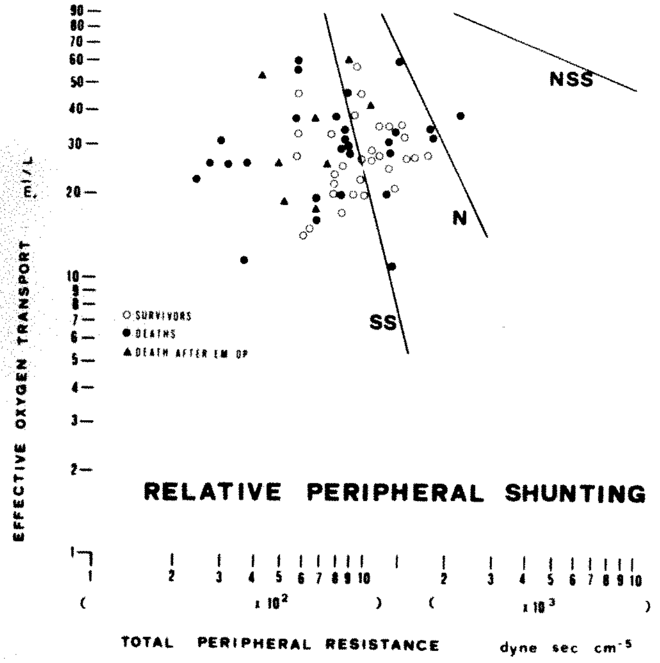


FIG. 4. Relative peripheral shunting in bleeding cirrhotic patients. Log-log plot of effective oxygen transport in milliliters of oxygen per liter of blood flow versus total peripheral resistance in dyne-sec-cm^{-5}.[12]

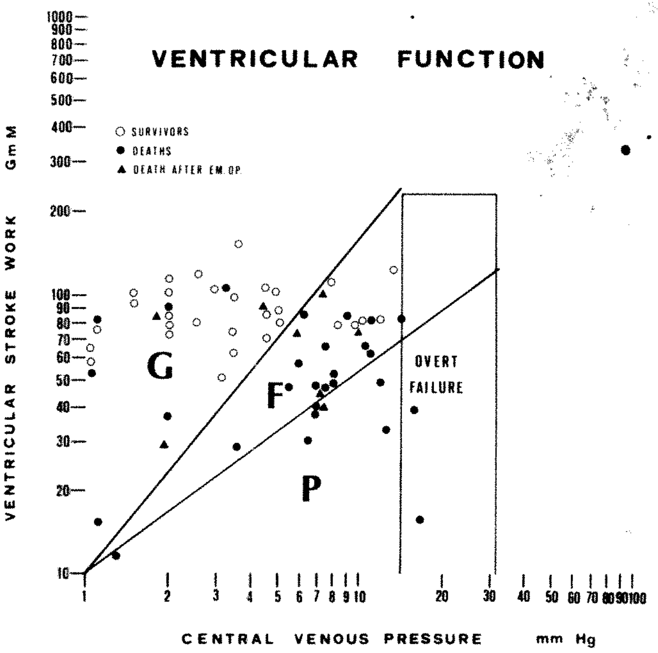


FIG. 5. Ventricular function relationships in bleeding cirrhotic patients. Log-log plot of left ventricular stroke work in gram meters versus central venous pressure in millimeters of mercury. The three regions of the graph, indicated by Good, Fair, and Poor, represent the different levels of ventricular function.[12]

The study of the correlation between effective oxygen transport and total peripheral resistance (Fig. 4) shows that 48–72 hours after hemorrhage the cirrhotic patients develop a progressive increase in peripheral shunting. The further decreased the index is compared to the mean slope for patients in septic shock, the higher was the cirrhotic patients mortality. The area of greatest risk was delimited by EOT ≤ 30 ml/l and TPR ≤ 700 dyne/sec/cm^{-5} (10 patients out of 13 died).

Ventricular function. When left ventricular stroke work is plotted against central venous pressure (Fig. 5), it can be seen that in more than half the cirrhotic patients myocardial function is depressed (fair and poor range). All patients in the Poor range died, while mortality was 75% in the Fair range and 27.2% in the Good range. These data suggest that the level of ventricular function has the major prognostic significance.

Histological Findings

Of the 66 patients comprising the above study, 19 belonged to the histological Group II, 8 to III, 22 to IV *m*oderate, 17 to IV *s*evere. Progressive lethality occurred with increasing severity in liver damage. The mortality rate was 21% in Group II, 37% in III, 68.1% in Group IV*m* and 82.3% in IV*s*. Eight of the 15 patients

TABLE 2. *Influence of the Degree of Liver Lesions on Mortality and on Causes of Death Following Emergency and Elective Portacaval Shunt*

Histologic Groups	Emergency Surgery No. of Patients	No. of Deaths	Causes of Death	Delayed Surgery No. of Patients	No. of Deaths	Causes of Death
I	5	1	Rebleeding	6	—	—
II	10	3	2 septic shock 1 rebleeding	23	1	1 renal failure
III	7	1	Rebleeding	17	2	2 rebleeding
IV moderate	6	4	4 hepatic coma	9	3	3 hepatic coma
IV severe	9	9	9 hepatic coma	—	—	
Total	37	18		55	6	

operated urgently died. Among them 6 belonged to the Group IV, one to II and one to Group III. The survivors were 2 patients from Group II, 4 patients from Group III and only one patient from group IV*m*.

Table 2 illustrates the influence of the grade of histologic alteration of the liver to the postoperative mortality, in a larger series of patients operated during the same period of study. It was comprised of cases who had undergone hepatic biopsy before the elective intervention. In patients belonging to Group IV, urgent surgery gives poor results (87%), but the mortality is high (33%), even in elective operations.

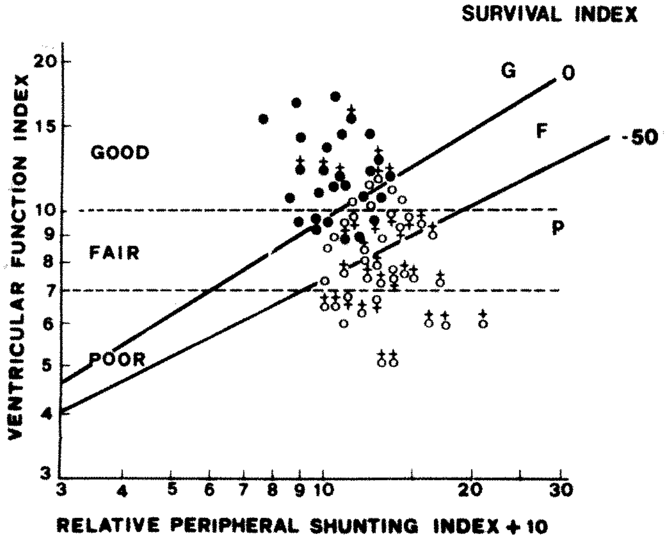


FIG. 6. Correlation between histological findings and hemodynamics. Open circles represent group IV patients while closed circles represent group II and III patients. (There were no group I patients studied hemodynamically.) The interplay between relative peripheral shunting index and ventricular function index reflects the reserve capacity of the cardiovascular system (survival index). Deaths indicated by crosses. The three regions of *S*urvival *I*ndex based on the studies of Siegel[12] are shown. In this study patients in the *G* region (SI > 0) had a 72% survival, patients in the *F* region (SI > −50 to 0) had a 55% survival, and patients in the *P* region (SI < −50) had a survival of only 11%. This graph shows clearly the correlation of cardiovascular and hepatic pathologic abnormalities.

The causes of death are different, based on the variation of histologic groups. Fourteen of the 16 patients belonging to group IV who died were comatose, while the causes of death in the other groups were sepsis, rebleeding and renal failure. The histological results have also been correlated to the Survival Index (Fig. 6).[12]

Survival Index

In previous studies[11,12] it was shown that the *preoperative* patterns of cardiovascular hemodynamics and oxygen consumption could be used to predict the probability of survival after portal decompression surgery. The best synthesis of these data into an information rich graphic display was achieved by developing an algorithm which enabled the plotting of the Ventricular Function Index (Fig. 5) as a function of the index of Relative Peripheral Shunting (Fig. 4).[12] This is seen in Figure 6 which also shows the three prognostic survival regions (Good > 50%, Fair > 20% < 50%, and Poor < 20%) derived by Siegel and Williams.[12] In physiologic terms, the interpretation of this relationship is that to survive, a cirrhotic patient whose peripheral abnormalities of vascular tone and oxygen extraction are small (as measured by the Relative Peripheral Shunting Index), does not require as good a level of Ventricular Function, as a patient whose peripheral abnormalities are great.

This hypothesis is confirmed by our data which shows a 72% survival for patients whose lowest preoperation study placed them in the Good (G) region, a 55% survival for patients in the Fair (F) region, but only an 11% survival for patients in the Poor (P) region. However, our data extend their observations[12] by clearly demonstrating that the hemodynamic and metabolic abnormalities reflected in the Survival Index are directly correlated with the nature and magnitude of the histologic pathology seen on liver biopsy. This is also shown in Figure 6 where the group IV histologic grade biopsied patients (open circles) are seen to lie almost exclusively in the F and P regions and the combination of poor histology and poor physiology (histologic group IV and Survival Index in Poor region) produced the highest mortality.

Discussion

The value of emergency surgery in the treatment of bleeding from esophageal varices continue to be a matter of debate. Many of the criteria used to evaluate cirrhotic patients have shown no significant correlation with survival. Child's classification,[1] based on clinical and laboratory data, still provides a good basis for patient selection for elective surgery, but it is not very useful for evaluating the bleeding patient. Also, a better knowledge of the hemodynamics of the splanchnic circulation has not helped to improve patient selection in terms of better survival rates.[10] These considerations led Orloff et al.[8,9] to perform emergency operations on all patients with bleeding varices due to alcoholic cirrhosis, his only contraindication to emergency portacaval shunt being the combined presence of ascites, icterus, encephalopathy and severe muscle wasting. However, this approach resulted in an unacceptable mortality rate.

The study of cardiovascular hemodynamics and liver biopsy appear to be a more valid criteria for surgical prognosis and thus for rational treatment of cirrhotic patients bleeding from esophageal varices. Systemic manifestations of hepatic cirrhosis have been studied by Del Guercio[2] and Siegel:[11] these authors have shown that some cardiovascular aspects assume remarkable prognostic significance for hemorrhage and stress due to surgery.

Recent observations by Siegel et al.[13,14] have extended the description of the hyperdynamic states that characterize the circulatory response patterns in cirrhotic liver disease. Three types of hyperdynamic responses exist. In stable patients with good liver function there is only a slight increase in the cardiac index with minimal alterations in vascular tone (R state). In patients under greater stress from hemorrhage with some acute hepatic decompensation there is a great increase in cardiac index and heart rate, with minimal decrease in mean blood pressure, which signifies a reduction in peripheral vascular tone. However, arteriovenous oxygen extraction is normal, so that total oxygen consumption is increased and a physiological correlation exists between oxygen supply and demand (A state or balanced hyperdynamic response).

In the third group of cirrhotic patients the distinguishing features consist of the narrowing of the arteriovenous oxygen content difference and the corresponding rise of the mixed venous oxygen tension. Although the increase in cardiac index is large, vascular tone is markedly decreased and the resultant increase in peripheral flow is not able to compensate for reduced O_2 extraction and total oxygen consumption falls (B state or unbalanced hyperdynamic response). A small group of the B state patients may also manifest a decompensated pattern and transition into a state of respiratory insufficiency (C state). There is also a great tendency for the B state patient with abnormal vascular tone and low oxygen consumption to develop a state characterized by myocardial failure similar to that seen in patients with cardiogenic shock (D state), at which point cardiac output falls and death frequently ensues unless major inotropic therapy can be used.

A major acute stress such as hemorrhage is usually the stimulus for a change from one compensation state to another. The hypovolemic phase of an acute hemorrhage produces a low cardiac output acutely, but after resuscitation the characteristic hyperdynamic response states are seen as a function of the degree of acute and chronic liver injury. In this phase a clear deterioration of the hemodynamic and metabolic parameters occurs with a marked reduction in vascular tone, the appearance of a reduced arteriovenous oxygen extraction, and a worsening of ventricular function. In this phase the hemodynamic study acquires precise prognostic significance, and there are clear cardiovascular differences between patients who die and those who survive (Figs. 2–6). The cardiac function pattern seems particularly useful for prognosis: mortality is significantly different in the three areas of the ventricular function graph (Fig. 5): in our study 27% in "Good," 75% in "Fair" and 100% in "Poor." These data confirm that myocardial adequacy is a key factor in the cirrhotic patients in overcoming stress due to hemorrhage.[11] This becomes more important in proportion to the seriousness of the combined vascular tone and oxygen consumption abnormalities in the peripheral tissues (Fig. 4) and the vascular and myocardial abnormalities can be accurately quantified by the Survival Index (Fig. 6).[12]

Because of the great perfusion demands imposed by the marked reduction in vascular tone (Fig. 2), if the total blood flow cannot be maintained high by good cardiac function, the prognosis becomes grave. In our case histories, the patients who remained hypodynamic or normodynamic after 48 hours had a very high mortality rate (14 deaths in 16 patients). As previously shown[11] heart failure can occur even with a high cardiac output. This motivates our usage of inotropic agents (digoxin or a combination of isoproterenol and glucagon given by continuous intravenous infusion as proposed by Siegel et al.[13]) in all cirrhotic patients with a reduced arterial–venous oxygen content, given that their chance for survival depends on an adequate myo-

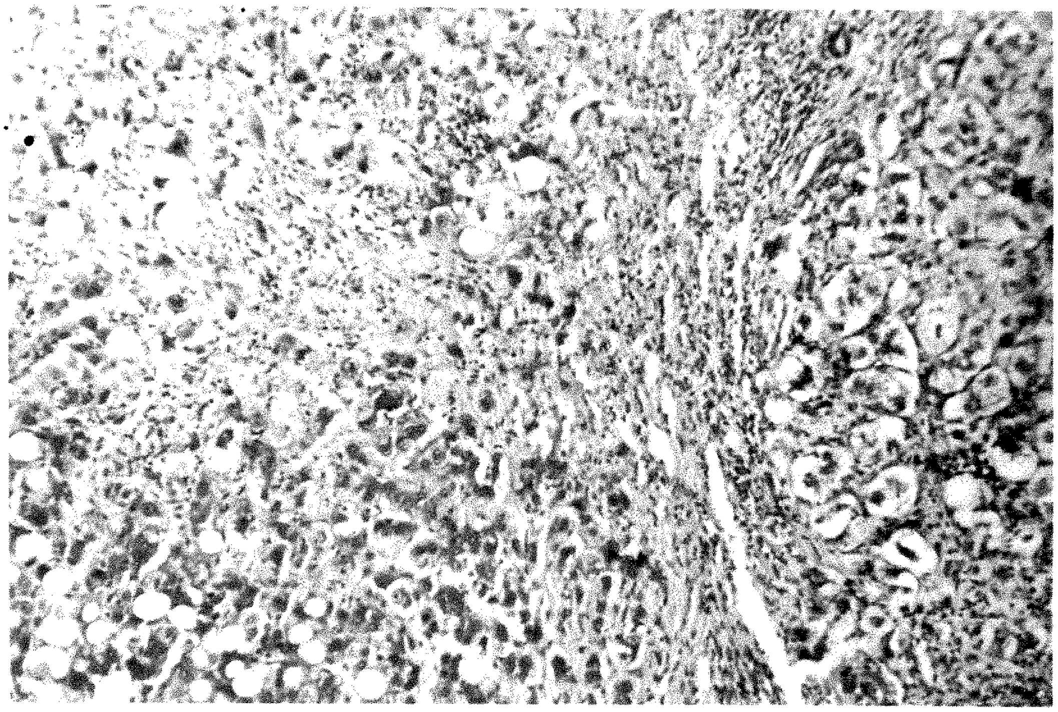


FIG. 7. Liver cirrhosis with acute alcoholic hepatitis: hyaline necrosis with Mallory bodies associated with sclerosis, edema, polymorphonuclear leukocytic infiltration and fatty metamorphosis.

cardial function. With regard to timing of surgery it is evident that progressive deterioration, despite medical support, of vascular tone, oxygen extraction and myocardial function, represents a strict contraindication to emergency portal decompression, since when all of these factors are combined the mortality approaches 100% (Fig. 6).

The second aim of our study was to investigate whether a preoperative liver biopsy is an important factor in determining the prognosis and indications for surgery, and whether correlations exist between the degree of liver changes and hemodynamics. Previous reports from Mikkelsen[6,7] indicate that the presence of acute hyaline necrosis in the hepatocyte adversely influences survival after portocaval shunt in cirrhotic patients. These authors recommend that a percutaneous liver biopsy must precede consideration of either an emergency or an elective shunt.

The standard anterior method of liver biopsy is not thought possible in all bleeding patients due to the problems imposed by coagulation deficits. For this reason we have executed needle-biopsy using an approach which is shown to be safer. The posterior approach permits an extraperitoneal liver biopsy through the costal-diaphragmatic sinus, the diaphragm, and the right coronary ligamentum. This technique can be utilized not only in the patient with ascites but also when intense jaundice and grave coagulation deficits are present, since the connective tissue at the level of the insertion of the coronary ligament of the diaphragm is very compact and does not permit the outflow of an eventual bile or hemorrhagic collection.

Our microscopic study of the liver differs from that of Mikkelsen,[6,7] in that histologic aspects other than hyaline necrosis are considered. Indeed, hyaline necrosis represents only 30% of the alterations found in histologic Group IV. In this group are seen three different histologic aspects of the same level of gravity. These correspond to acute alcoholic hepatitis, acute viral hepatitis and hepatitis of ischemic type which is observed in major hemorrhage.

The first histologic pattern is that described by Mikkelsen et al.[5] It is characterized by the hyaline necrosis, typical Mallory bodies, and grave steatosis with a polymorphonuclear leucocytic infiltration (Fig. 7).

The second pattern shows extensive necrosis of the hepatic parenchyma, Councilman bodies, grave cellular pleomorphism, and eosinophilic degeneration of the hepatic cells. The third pattern seen in acute ischemic hepatopathology is characterized by necrosis of an eosinophilic type with cystoplasmic retraction, a loss of cellular limits and intense perisinusoidal edema (Fig. 8).

The overall mortality in the 66 patients series considered in this study was directly proportional to the gravity of hepatic lesions. That is 21% for Group II patients, 37.5% for Group III and 68.1% and 82.3% for patients belonging to histologic alteration groups IV *m*oderate and IV *s*evere respectively.

In Group IV patients any surgical program is contraindicated. The already gravely injured liver cells cannot support any further damage produced by surgical trauma, by anaesthetics or by hemodynamic changes due to surgical shunts. As can be seen in Table 2,

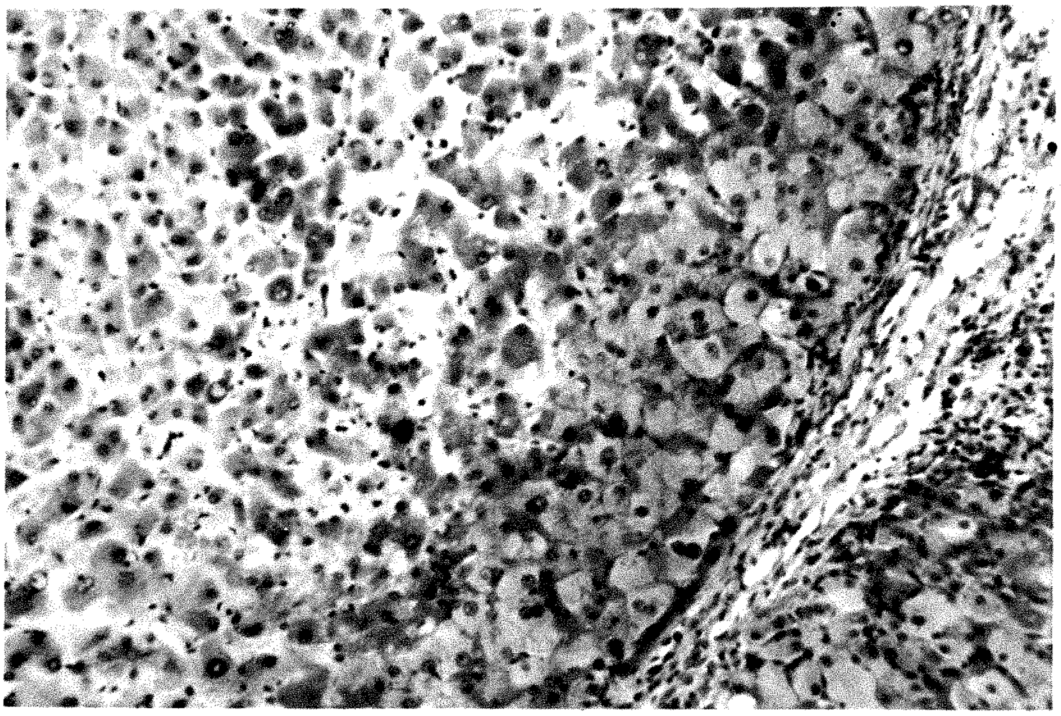


FIG. 8. Liver cirrhosis with acute severe parenchymal lesions of ischemic origin: eosinophil necrosis with cytoplasmic condensation and loss of cellular limits, centrolobular perisinusoidal edema.

such patients do poorly after emergency operations, 13 out of 15 Group IV patients (87%) died, but mortality was also high (33%) in elective operations. Moreover, all Group IV patients died in hepatic coma, while the causes of death in the other histologic groups were sepsis, rebleeding or renal insufficiency. In non-operated bleeding patients in Group IV the mortality rate was also 71.8%, but with time the lesion can be reversible and the survivors will then be better operative candidates.

The final aspect of this study takes account of the relationship existing between the hemodynamic alterations and histologic aspects. Consideration of the more important aspects of the physiologic response to hemorrhage in the cirrhotic patient, the relative peripheral shunt and the ventricular function shows that there exists a major difference in the pattern of physiologic response in patients of histologic Group IV compared to those in Groups II and III. The Group IV patients have a lower vascular tone and a reduced oxygen extraction, thus a greater index of relative peripheral shunting than patients with more favorable histology. However, most important in the group IV patients is the fact that cardiac function (the ventricular function index) is significantly more depressed with respect to the patients in the other two histologic groups. This disproportionate reduction in myocardial capacity with respect to the degree of abnormality in relative peripheral shunting is reflected in the lower values of Survival Index (SI) (Fig. 6) observed in these patients ($SI \leq 0 > -50$ equaled 55% survival, $SI \leq -50$ equaled 11% survival).

These findings confirm the utility of hemodynamic staging in the preoperative evaluation of cirrhotic patients with bleeding esophageal varices as a critical predictor of the short-term survival prognosis and as a means following the improvement in post operative course.[12] They also confirm the premise that the adequacy of liver function plays the fundamental role in conditioning the gravity of the cardiovascular and metabolic abnormalities found in the cirrhotic patient.[13,14] The true mechanical shunting of portal blood plays a role of minor importance in hemodynamic compensation, as demonstrated by patients with prehepatic block and normal liver histology in whom the hemodynamic alterations do not even reach the gravity observed in stable cirrhotic patients *without* variceal hemorrhage.

Summary

The adequacy of cardiovascular hemodynamics and the degree of normality of the histological study of the liver are the most valid criteria for survival prognosis and rational treatment of the cirrhotic patient bleeding from esophageal varices. These criteria were applied to the study of 66 cirrhotic patients during hemorrhage, 15 of whom underwent emergency portal decompression. The time course evaluation of hemodynamic parameters was made using the method of cardiovascular evaluation developed by Siegel and associates.[11,12] Within 48 hours after the onset of hemorrhage and following volume replacement the hemodynamic and metabolic pattern changes noticeably and acquires

precise prognostic significance. There is a marked reduction of Vascular Tone which relates cardiac index and peripheral resistance, a narrowing of the arteriovenous oxygen content difference and a worsening of Ventricular Function which relates cardiac stroke work and right atrial pressure. The pattern of cardiac function viewed in the light of the peripheral abnormalities in vascular function (Survival Index) is particularly useful for prognosis.

Percutaneous needle biopsies were also done in all patients in whom hemodynamics were evaluated, using a posterior extraperitoneal approach. As a result of the histological studies of the liver, the cirrhotic patients were classified into four groups (I, II, III, IV) of increasing pathologic abnormality. Group IV was characterized by severe degenerative lesions and parenchymal necrosis (chronic liver disease with important acute superimposition of alcoholic, viral or ischemic injury). Almost all patients in Group IV who underwent emergency surgery died during the postoperative period with liver failure. In nonoperated Group IV patients the mortality was 71%, but with time these acute histologic lesions are reversible and survivors will then be good operative candidates, similar to patients in the other histologic groups. A strong positive correlation exists between the extent of the pathologic changes in the liver biopsy and the degree of hemodynamic impairment.

References

1. Child, C. G. and Turcotte, J. G.: The surgery of portal hypertension, *In* Child, C. G. (ed.) The Liver and Portal Hypertension. Philadelphia, W. B. Saunders Co., 1964.
2. Del Guercio, L. R. M., Coomaraswamy, R. P., Feins, N. R., et al.: Pulmonary Arteriovenous Admixture and the Hyperdynamic Cardiovascular State in Surgery for Portal Hypertension. Surgery, 56:57, 1964.
3. Fisher, J. E.: Hepatic Coma in Cirrhosis, Portal Hypertension and Following Portacaval Shunt. Its Etiologies and the Current Status of its Treatment. Arch. Surg., 108:325, 1974.
4. Greenspan, M. and Del Guercio, L. R. M.: Cardiorespiratory Determinants of Survival in Cirrhotic Patients Requiring Surgery for Portal Hypertension. Am. J. Surg., 115:43, 1968.
5. Mikkelsen, W. P., Turrill, F. L. and Kern, W. H.: Acute Hyaline Necrosis of the Liver. Am. J. Surg., 116:266, 1968.
6. Mikkelsen, W. P.: Therapeutic Portacaval Shunt. Preliminary Data on Controlled Trial and Morbid Effects of Acute Hyaline Necrosis. Arch. Surg., 108:303, 1974.
7. Mikkelsen, W. P. and Kern, W. H.: The influence of acute hyaline necrosis on survival after emergency and elective portacaval shunt, *In* Child, C. G. (ed.) Portal Hypertension. Philadelphia, W. B. Saunders, Co., 1974. p. 233.
8. Orloff, M. J., Charters, A. C., Chandler, J. G., et al.: Portacaval Shunt as Emergency Procedure in Unselected Patients with Alcoholic Cirrhosis. Surg. Gynecol. Obstet., 141:59, 1975.
9. Orloff, M. J., Duguay, L. R. and Kosta, L. D.: Criteria for Selection of Patients for Emergency Portacaval Shunt. Am. J. Surg., 134:146, 1977.
10. Reynolds, T. B.: The Role of Hemodynamic Measurements in Portosystemic Shunt Surgery. Arch. Surg., 108:276, 1974.
11. Siegel, J. H., Greenspan, M., Cohn, J. D. and Del Guercio, L. R. M.: The Prognostic Implications of Altered Physiology in Operations for Portal Hypertension. Surg. Gynec. Obstet., 126:249, 1968.
12. Siegel, J. H. and Williams, J. B.: A Computer-based Index for the Prediction of Operative Survival in Patients with Cirrhosis and Portal Hypertension. Ann. Surg., 169:191, 1969.
13. Siegel, J. H., Goldwyn, R. M., Farrell, E. J., et al.: Hyperdynamic States and the Physiologic Determinants of Survival in Patients with Cirrhosis and Portal Hypertension. Arch. Surg., 108:282, 1974.
14. Siegel, J. H.: The surgery of cirrhotic liver disease with portal hypertension, *In* Siegel, J. H. and Chodoff, P. D. (eds.) The Aged and High Risk Surgical Patient. New York, Grune & Stratton Inc., 1976, p. 797.
15. Staudacher, V. and Bevilacqua, G.: A New Method for Radical Treatment of Esophagogastric Varices. Urg. Chir. Comment., 1:65, 1978.

Intravascular Coagulation and Fibrinolysis within Primate Extremities During Tourniquet Ischemia

STEPHEN H. MILLER, M.D., M. ELAINE EYSTER, M.D., ABDUS SALEEM, M.D., LARRY GOTTLEIB, M.D.,
DAVID BUCK, M.S., WILLIAM P. GRAHAM, III, M.D.

A common although infrequently recognized complication associated with the use of a pneumatic tourniquet is profuse bleeding from the wound after deflation of the tourniquet. The purpose of this study was to determine whether intravascular coagulation and fibrinolysis could be induced in subhuman primates by tourniquet ischemia, and whether this phenomenon could be altered by pretreatment of the animal with heparin. It was shown that, after 2½ hours of tourniquet ischemia, (400 mmHg) to one lower limb, fibrinogen levels were significantly lower ($p < .005$), antithrombin III levels were significantly lower ($p < .05$), plasminogen levels were significantly lower ($p < .05$), fibrin split products significantly higher ($p < .025$) and fibrinopeptide A levels were significantly higher ($p < .02$) than values measured simultaneously in the control limbs. After pre-treatment with sodium heparin, 30 units/kg, there was no change in antithrombin III levels or fibrinogen levels, but fibrin split products in the experimental limbs were significantly elevated ($p < .05$) when compared to control limbs. In both groups the abnormal levels returned to control levels 5–30 minutes after tourniquet deflation. We conclude that intravascular coagulation and fibrinolysis develop within ischemic subhuman primate limbs during tourniquet ischemia. Pretreatment with heparin prevents the consumption of fibrinogen and antithrombin III but does not prevent the increase in fibrin split products which was observed. It is possible that intravascular coagulation and fibrinolysis contribute to post tourniquet bleeding.

A COMMON ALTHOUGH INFREQUENTLY recognized complication associated with the use of a pneumatic tourniquet is profuse bleeding from the wound after deflation of the tourniquet. This phenomenon has been attributed to the reactive hyperemia which develops after tourniquet ischemia, but its true etiology is obscure.[5]

The purpose of this study was to determine whether intravascular coagulation and fibrinolysis could be detected within subhuman primate limbs during tourniquet ischemia, and whether this phenomenon could be altered by pre-treatment of the animal with heparin.

From the Departments of Surgery, Medicine and Pathology, The Milton S. Hershey Medical Center of the Pennsylvania State University, Hershey, Pennsylvania

Methods

Part I

Ivy bleeding times were performed and venous blood samples were drawn from groups of ten stump tailed monkeys. Specimens were taken from awake animals and monkeys anesthetized with intravenous sodium pentobarbital alone or in combination with intravenous infusion of sodium heparin, 30 units per kg.

Three layers of three inch wide cotton bandage were wrapped circumferentially around the mid-thigh of one lower extremity, and a pneumatic tourniquet was inflated to 400 mm of mercury for 2.5 hours. Tourniquets were calibrated daily with a mercury manometer. Bleeding times were repeated and venous blood samples were collected from each lower extremity during tourniquet ischemia and at varying intervals following tourniquet deflation. Because no more than 5 ml of free flowing blood could be obtained from the edematous ischemic limb, a series of separate experiments was carried out. In each series, blood samples from ten monkeys were aliquoted into polystyrene tubes containing the appropriate anticoagulant. For routine coagulation studies, nine parts blood plus one part 3.8% sodium citrate were placed on ice for no more than two hours until the platelet-poor plasma was separated in a refrigerated centrifuge. Paired specimens of plasma prepared in this manner from ischemic and control limbs were assayed within two hours of collection or stored frozen at −80°. Hematocrit determinations and platelet counts were performed immediately after each series of experiments. Ivy bleeding times were performed using a BD long-point microlance (Becton-Dickinson, Rutherford, N.J.). Fibrinogen determinations were performed on citrated plasma by

---

Reprint requests: Stephen H. Miller, M.D., Division of Plastic Surgery, The Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033.

Submitted for publication: February 21, 1979.

0003-4932/79/0800/0227 $00.70 © J. B. Lippincott Company

TABLE 1. *Control Values in Experimental Animals Prior to Tourniquet Ischemia*

	Awake	Anesthetized	Anesthetized Heparinized
Hematocrit (%)	37 ± 1.3 (6)	36 ± 0.8 (10)	37 ± 1 (8)
Platelet Count (× 10^3/cu mm)	423 ± 36 (10)	437 ± 35 (11)	422 ± 33 (9)
Bleeding Time (min)	3.1 ± 0.2 (10)	3.6 ± 0.4 (8)	3.5 ± 0.7 (8)
Fibrinogen (mg/dl)	246 ± 30 (9)	216 ± 11 (10)	236 ± 30 (8)
Fibrin Split Products (μg/ml)	6.4 ± 0.8 (10)	7.0 ± 0 (11)	8.0 ± 1 (9)
Antithrombin III (%)	122 ± 5.2 (8)	116 ± 6 (10)	118 ± 5.5 (8)

Values expressed as mean ± 1 SEM.

Numbers in parentheses represent the number of specimens used for each determination.

a modification of the turbidimetric clotting technique of Ellis and Stransky, according to the method of Saleem et al.[16] Antithrombin III was measured in plasma by the two stage method of Ødegard which measures thrombin neutralization in the presence of a chromogenic substrate.[12] Fibrin split products were measured in serum from blood clotted in the presence of small amounts of enzyme inhibitor, thrombin and reptilase, using the Thrombo-Wellcotest® rapid latex test kit (Burroughs Wellcome Co., Research Triangle Park, N.C.).

Part II

Fibrinopeptide A levels were measured in platelet-poor plasma which was flash frozen and shipped on dry ice to Dr. Hymie Nossel at the Columbia Presbyterian Medical Center. For this test, 5 ml of blood was mixed with 0.5 cc of anticoagulant containing 100 mg heparin and 1,000 units Trasylol (aprotinin buffer).[9] Plasminogen determinations were performed on acidified neutralized plasma by the caseinolytic method using oxalated plasma.[1] Results from ischemic limbs and control limbs were compared using the Student's paired t-test.

Results

Part I (Tables 1–3)

Normal control values prior to tourniquet ischemia are shown in Table 1. No significant alterations occurred in the hematocrits, platelet counts, bleeding times, fibrinogen levels, levels of fibrin split products or antithrombin III levels as a result of the administration of sodium pentobarbital alone or in combination with heparin.

However, after 2½ hours of tourniquet ischemia, fibrinogen levels fell to 168 mg/dl compared to 235 mg/dl in the control limbs ($p < .005$), antithrombin III levels dropped to 95% compared to 119% ($p < .05$), and fibrin split products increased to 19.4 μg/ml compared to 7.7 μg/ml ($p < .025$) in the control limbs. (Table 2, Group A). Mean platelet counts decreased by 20% in the ischemic limbs, but they were not significantly lower than those measured prior to tourniquet ischemia in either leg, or to those measured in the control limbs after tourniquet ischemia. Within five minutes after tourniquet deflation, all parameters had returned to normal. Hematocrits and bleeding times remained stable throughout the course of the experiment.

In animals receiving heparin, no significant changes occurred in fibrinogen or antithrombin III levels when compared to the control limbs (Table 2, Group B). However, fibrin split products remained elevated during tourniquet ischemia. Five minutes following tourniquet deflation, fibrin split products returned to control levels.

Comparison of the coagulation studies from the two sets of experimental limbs revealed that blood from

TABLE 2. *Coagulation Studies Following Tourniquet Ischemia*

	Control Limb	Experimental Limb After 2½ Hours of Ischemia	p Value	Experimental Limb 5 Minutes After Tourniquet Deflation
		Nonheparinized Group A		
Fibrinogen (mg/dl)	235 ± 14 (10)	168 ± 13.8 (8)	<.005	234 ± 13.1 (8)
Fibrin Split Products (μg/ml)	7.7 ± 0.7 (10)	19.4 ± 4.9 (10)	<.025	7.5 ± 0.9 (10)
Antithrombin III (%)	119 ± 4.7 (10)	95.5 ± 8.9 (8)	<.05	122 ± 4.6 (8)
		Heparinized Group B		
Fibrinogen (mg/dl)	282 ± 38 (6)	236 ± 28 (8)	NS	226 ± 24.8 (8)
Fibrin Split Products (μg/ml)	7.9 ± 1.0 (6)	19.5 ± 5.4 (8)	<.05	8.1 ± 1.1 (8)
Antithrombin III (%)	128 ± 3.6 (6)	119 ± 5.6 (8)	NS	131 ± 5 (8)

TABLE 3. *Comparison of Experimental Limbs in Nonheparinized Versus Heparinized Animals*

	Nonheparinized Group A	Heparinized Group B	p Value
Fibrinogen (mg/dl)	168 ± 13.8 (8)	236 ± 27.8 (8)	<.02
Fibrin Split Products (μg/ml)	19.5 ± 4.9 (10)	19.5 ± 5.4 (8)	NS
Antithrombin III (%)	95.5 ± 8.9 (8)	119 ± 5.6 (8)	<.01

TABLE 4. *Fibrinopeptide A Levels in Nonheparinized Animals*

	Control Limb	Experimental Limb	p Value
Preischemia	22 ± 0.2 pmoles/ml		
During ischemia 2½ hours duration	14.9 ± 6.03 (9)	158 ± 52 (9)	<.02
30 minutes after ischemia	7.9 ± 1.7 (8)	15.7 ± 45 (9)	NS
24 hours after ischemia	3.8 ± 2.4 (6)	3.0 ± 1.1 (6)	NS

the heparinized ischemic limbs had a significantly higher fibrinogen level and antithrombin III concentration than blood from nonheparinized limbs (Table 3). No significant differences were noted in the fibrin split products from the two sets of experimental limbs.

Part II (Tables 4 and 5)

To investigate whether these changes were due to intravascular coagulation, fibrinopeptide A levels were measured in a group of nine animals. As can be seen in Table 4, after 2½ hours of tourniquet ischemia, fibrinopeptide A levels were 158 pmoles/ml in the ischemic limbs compared to 14.9 pmoles/ml in the control limb ($p < .02$). Values returned to normal within 30 minutes after release of the tourniquet.

Finally, to confirm that the elevated fibrin split products were due to the activation of plasminogen, plasminogen levels were measured in a group of six animals under similar experimental conditions, except that samples were drawn from the femoral vein proximal to the tourniquet immediately after release of the tourniquet. This modification in technique was necessary because of difficulty obtaining access to superficial veins which become fibrotic with repeated use. As can be seen in Table 5, plasminogen levels were 9.1 nkat units in the experimental limbs compared to 24 nkat units in the control limb ($p < .05$).

Discussion

Potential hazards associated with the use of a pneumatic tourniquet include direct injury to local tissues by compression and injury to tissues distal to the tourniquet because of ischemia, hypoxia and acidosis.[6,14,18–20] Tissue thromboplastin which is released after injury causes activation of the extrinsic system of blood coagulation.[13] Ischemia, hypoxia and acidosis also produce injury to the vascular endothelium and activate the intrinsic system of coagulation as well as the fibrinolytic system.[3,11]

Some authors have demonstrated that a bleeding tendency secondary to tourniquet use develops in rats and dogs after prolonged ischemia.[8,15] Paletta et al. noted that the limbs of dogs treated with heparin prior to and during tourniquet ischemia (600–650 mmHg for five hours) had more rapid "normalization" of skin and muscle temperature, less local edema and did not develop foot drop as did the nonheparinized group.[14] Strock and Majno were unable to find evidence of intravascular coagulation within rat limbs subjected to tourniquet ischemia for hours.[17,18] Eriksson et al. have observed vascular thrombosis within the vasculature of the tenuissimus muscle after six hours of tourniquet ischemia to the hind limb of a cat.[2] Wilgis reported that, after 1½ hours of tourniquet ischemia in human beings, prothrombin times in blood samples drawn from ischemic limbs were 70–75% normal and partial thromboplastin times were prolonged.[19,20]

Our studies clearly indicate that during tourniquet ischemia (400 mgHg for 2½ hours) intravascular coagulation develops within the ischemic limbs of subhuman primates. Significant decreases in fibrinogen and antithrombin III levels prevented by heparin support this conclusion, despite the fact that the platelet counts, while lower, were not significantly less than in control limbs.

Further credence for the diagnosis of consumptive coagulopathy is lent by the markedly elevated fibrinopeptide A levels measured in the experimental limbs after 2½ hours of tourniquet ischemia. Fibrinopeptide A is released when thrombin cleaves the Aα chain of fibrinogen.[10] Thus as a direct index of thrombin action, it is a highly specific and extremely sensitive test for intravascular coagulation.

The significant decrease in plasminogen and the rise in fibrin split products is evidence that plasminogen activation was accompanying intravascular coagulation, as expected. However, intravascular coagulation

TABLE 5. *Plasminogen Levels after 2.5 Hours Tourniquet Ischemia*

	Control Limb	Experimental Limb†	p Value
Plasminogen*	24 ± 5 (6)	9.1 ± 1.8 (6)	<.05

* Normal values 18.6 ± 1.7 nkat units, n = 8.

† Specimens drawn from femoral vein proximal to tourniquet immediately after release of tourniquet in 5 of 6 animals.

with secondary fibrinolysis does not explain the increase in fibrin split products which was observed in the heparinized animals. It is possible that, in response to severe anoxic stimuli, plasminogen activator was released from damaged endothelial cells in sufficient quantities to overwhelm the normal inhibitory mechanisms, causing hyperplasminemia and proteolysis of circulating fibrinogen (*i.e.* primary fibrinolysis). Since plasmin levels were not measured, we cannot exclude this possibility. However, the insignificant change in fibrinogen suggests that primary fibrinolysis was not the cause of the elevated split products in the heparinized animals. A more likely explanation is that nonplasmin fibrinolytic activies were also operative. These may include proteinases released by polymorphonuclear leukocytes, as well as other nonplasmin proteinases.[7]

The rapid return of fibrinogen, antithrombin III and fibrin split products to normal levels five minutes after tourniquet deflation is most likely due to the ingress of clotting factors from the systemic circulation, dilution of the fibrin split products, and removal of these products by the now-patent and functional venous system.

An alternative explanation for the decrease in platelet counts, fibrinogen, and antithrombin III levels, which must be considered is whether hemorrhage or hemodilution occurred during the course of the experiment.[4] These possibilities are not likely because the hematocrit remained stable, no bleeding occurred other than during removal of blood samples (total volume was 30 cc), and no intravenous fluids which might have produced hemodilution were administered. Moreover, as stated previously, thrombin activity as measured by FPA generation was specifically increased.

Caution should be exercised in equating the coagulation abnormalities which developed after tourniquet ischemia to clinical bleeding since the observed changes in fibrinogen and platelet counts were not of a magnitude which would be expected to impair hemostasis. However, in association with ischemic changes and vasodilutation, bleeding might well be potentiated by consumption and fibrinolysis of this magnitude.

We conclude that intravascular coagulation and fibrinolysis manifested by a significant fall in fibrinogen, antithrombin III, and plasminogen levels, accompanied by a significant increase in fibrin split products and fibrinopeptide A levels develops within ischemic subhuman primate limbs during tourniquet ischemia. Pretreatment with heparin prevents the consumption of fibrinogen and antithrombin III but does not prevent the elevation of fibrin split products which was observed. It is possible that these changes in association with local ischemic changes may contribute to post tourniquet bleeding.

Acknowledgment

The authors wish to thank Dr. H. L. Nossel for the performance of the fibrinopeptide A analyses.

References

1. Bowie, E. J. W., Thompson, J. H., Jr., Didisheim, P. and Owen, C. A.: Mayo Clinic Laboratory Manual of Hemostasis. W. B. Saunders Company, Philadelphia, pp. 141–144, 1971.
2. Eriksson, E., Anderson, W. and Replogle, R.: Effects of Prolonged Ischemia on Muscle Microcirculation in the Cat. Surg. Forum XXV, 254, 1974.
3. Hardaway, R.: Shock and Disseminated Intravascular Coagulation. Thromb. Diath. Haemorr. Suppl., 20:121, 1966.
4. Herman, C., Moquin, R. and Horwitz, D.: Coagulation Changes of Hemorrhagic Shock in Baboons. Ann. Surg., 175:197, 1972.
5. Johnson, R. and Morain, W.: Hemostasis in Surgery of the Hand. Plast. Reconstr. Surg., 57:666, 1976.
6. Miller, S., Lung, R., Graham, W., III, et al.: The Acute Effects of Tourniquet Ischemia on Tissue and Blood Gas Tensions in the Primate Limb. J. Hand Surg., 3:11, 1978.
7. Moroz, L. A. and Gilmore, N. J.: Fibrinolysis in Normal Plasma and Blood: Evidence for Significant Mechanisms Independent of the Plasminogen-plasmin System. Blood, 48: 531, 1978.
8. Nakahara, M. and Sakahashi, H.: Effect of Application of a Tourniquet on Bleeding Factors in Dogs. J. Bone Joint Surg., 49A:1345, 1967.
9. Nossel, H.: Radioimmunoassay of Fibrinopeptides in Relation to Intravascular Coagulation and Thrombosis. N. Engl. J. Med., 295:428, 1976.
10. Nossel, H., Yudelman, I., Canfield, R., et al.: Measurement of Fibrinopeptide A in Human Blood. J. Clin. Invest., 54: 43, 1974.
11. O'Connell, T., Sanchez, M., Mowbray, J. and Fonkalsrud, E.: Effects on Arterial Intima of Saline Infusions. J. Surg. Res., 16:193, 1974.
12. Ødegard, O., Lie, M. and Abildgaard, U.: Heparin Cofactor Activity Measured with an Amidolytic Method. Thrombosis Res., 6:287, 1975.
13. Owen, C., Jr., Bowie, E., Didisheim, P. and Thompson, J., Jr.: Acquired hemorrhagic diseases. *In* C. A. Owen, Jr., E. J. Walker Bowie, P. Didisheim, and J. H. Thompson, Jr. (ed.) The Diagnosis of Bleeding Disorders. Boston, Little Brown and Company, 8:239–267, 1969.
14. Paletta, F., Shehadi, S., Mudd, J. and Cooper, T.: Hypothermia and Tourniquet Ischemia. PRS, 29:531, 1962.
15. Robinson, A., Holcroft, J., Olcott, C., IV and Blaisdell, F.: Pulmonary and Coagulation Changes in Tourniquet Shock. J. Surg. Res., 19:65, 1975.
16. Saleem, A., Krieg, A. and Fretz, K.: Improved Micromethod for Plasma Fibrinogen Unaffected by Heparin Therapy. Am. J. Clin. Pathol., 63:426, 1975.
17. Strock, P. and Majno, G.: Vascular Responses to Experimental Tourniquet Ischemia. Surg. Gynecol. Obstet., 129:309, 1969.
18. Strock, P. and Majno, G.: Microvascular Changes in Acutely Ischemic Rat Muscle. Surg. Gynecol. Obstet., 129:1213, 1969.
19. Wilgis, E. F. S.: Observations on the Effects of Tourniquet Ischemia. J. Bone Joint Surg., 53A:1343, 1971.
20. Wilgis, E. F. S.: Tourniquet ischemia, muscle anoxia, and operative edema. In *Symposium* on Reconstructive Hand Surgery, Vol. 9, J. W. Littier, L. Cramer and J. Smith, editors. St. Louis. C. V. Mosby, 5:59, 1974.

New Second Edition!

HERNIA

Edited by
Lloyd M. Nyhus, M.D.
and
Robert E. Condon, M.D.

Lippincott

J. B. LIPPINCOTT COMPANY
East Washington Square ● Phila., Pa. 19105

In Canada: J. B. Lippincott Company of Canada Ltd.
75 Horner Avenue, Toronto, Ontario M8Z 4X7

Please send me:
Nyhus & Condon: HERNIA 2nd Ed. $59.00

Name ______________________
Address ______________________
City ____________ State ______ Zip ______

☐ Payment enclosed (Save postage and handling)
☐ Charge and bill me (Plus postage and handling)

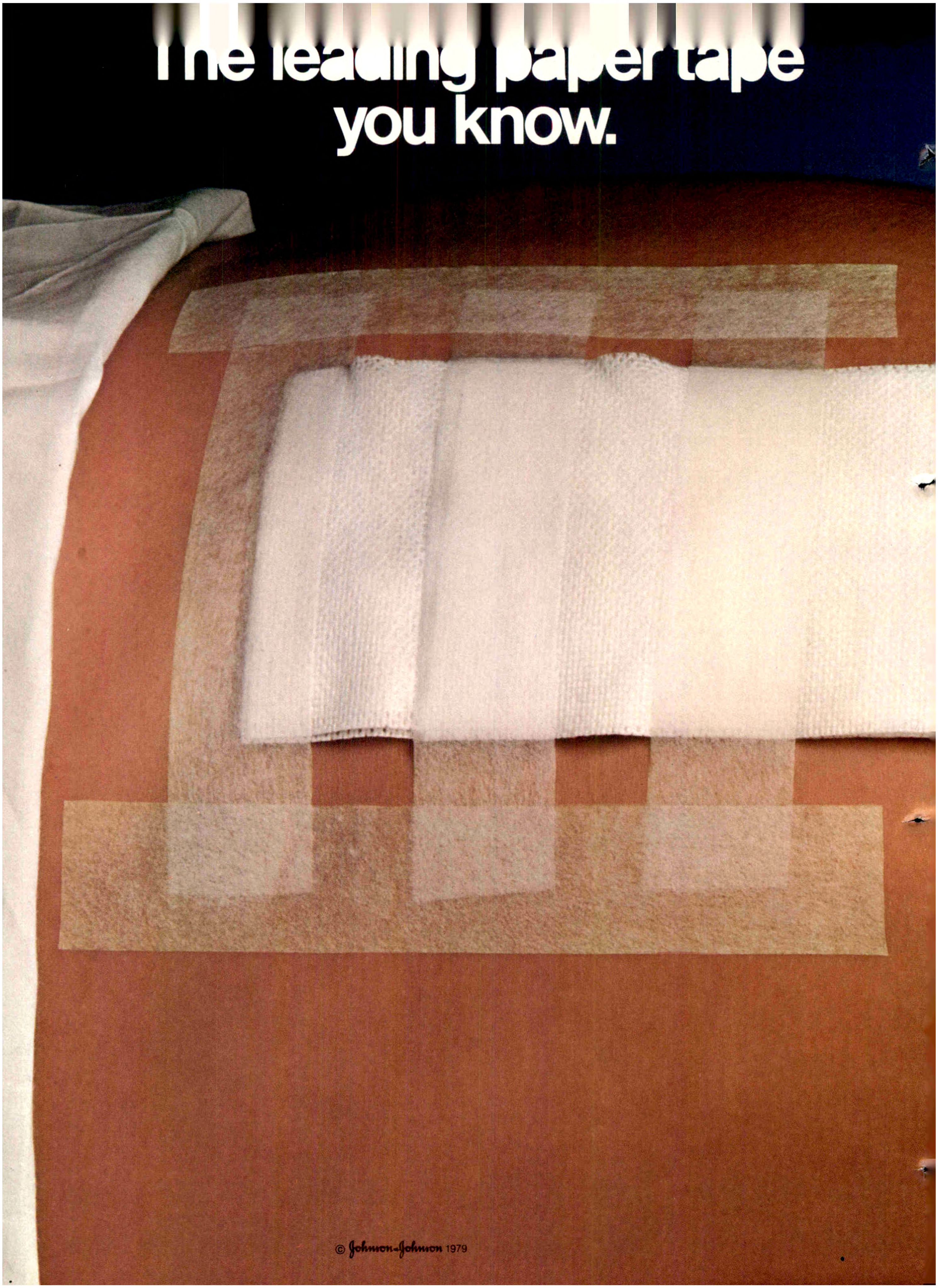
Also available at your medical bookstore. AS 8/79

"The book to end all books on hernia" . . . "Magnificent" . . . "recommended unreservedly" . . . "a summation of today's best total hernia knowledge" are just a small sampling of the international acclaim which greeted the publication of the first edition of this major work on hernia. Dr. Nyhus has now joined with a new co-editor, the noted surgeon Dr. Robert E. Condon, to bring this tremendous opus up-to-date in a *New (2nd) Edition.*

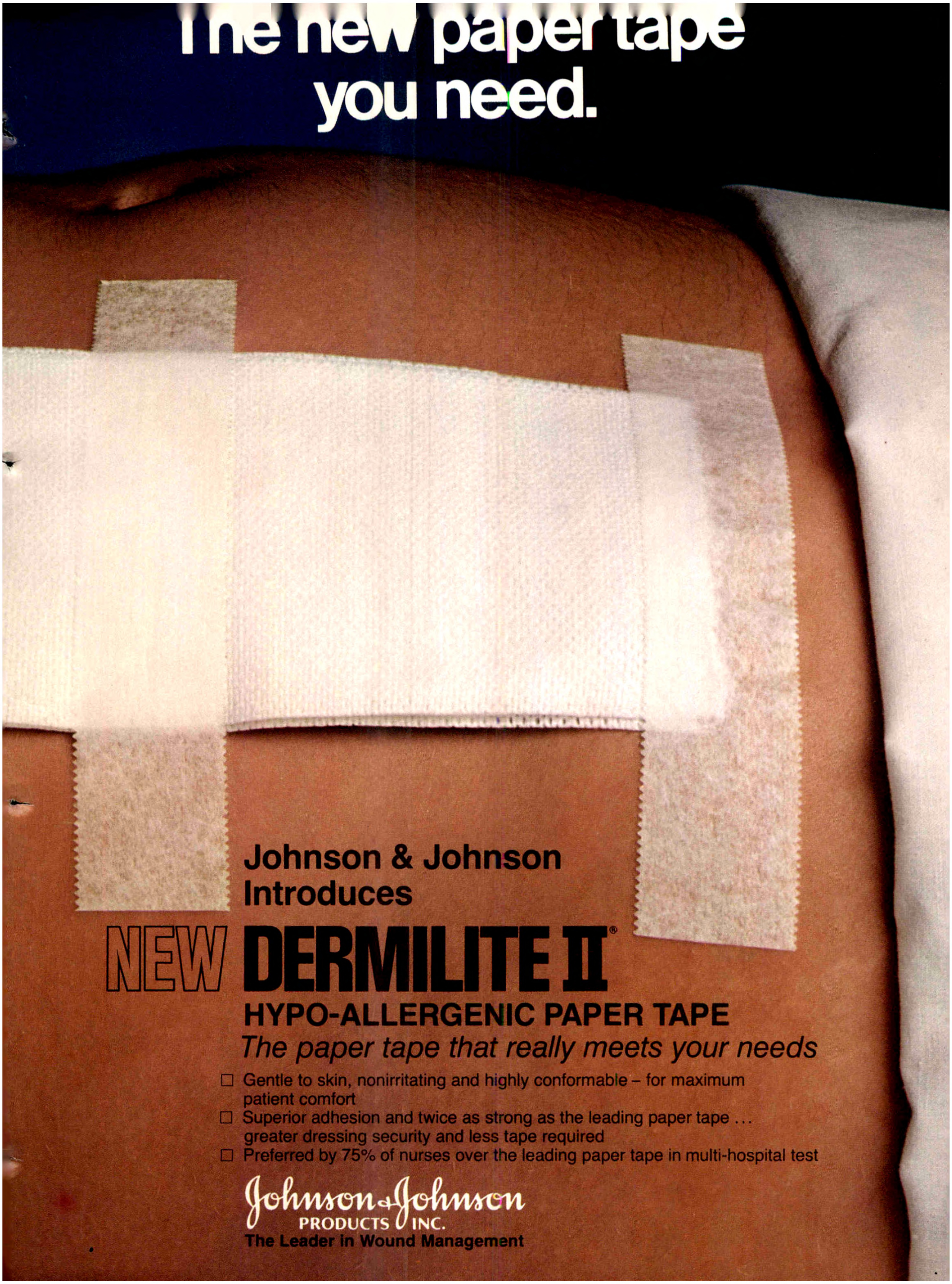
The many additions and revisions to this classic text fulfill the editors' goal of bringing together, in one definitive volume, all established and innovative concepts of hernial etiology, diagnosis, and repair. They reflect the current emphasis on specific types of hernias and certain therapeutic techniques. For example, of special interest in this edition is the considerably expanded section on hernias of the diaphragm, which represents the only truly comprehensive review of this clinically important condition that is presently available. A helpful discussion of the Shouldice approach and experience is also included.

The popular format of the original book has been retained, giving the readers the very best, most up-to-date information in every area of hernial surgery, from world-renowned contributors. The chapters are again followed by *Special Comments* from invited experts, followed by *Editorial Comments* by the editors.

782 Pages — 457 Illustrations
2nd Edition, 1978 — $59.00



© Johnson & Johnson 1979



**Johnson & Johnson
Introduces**

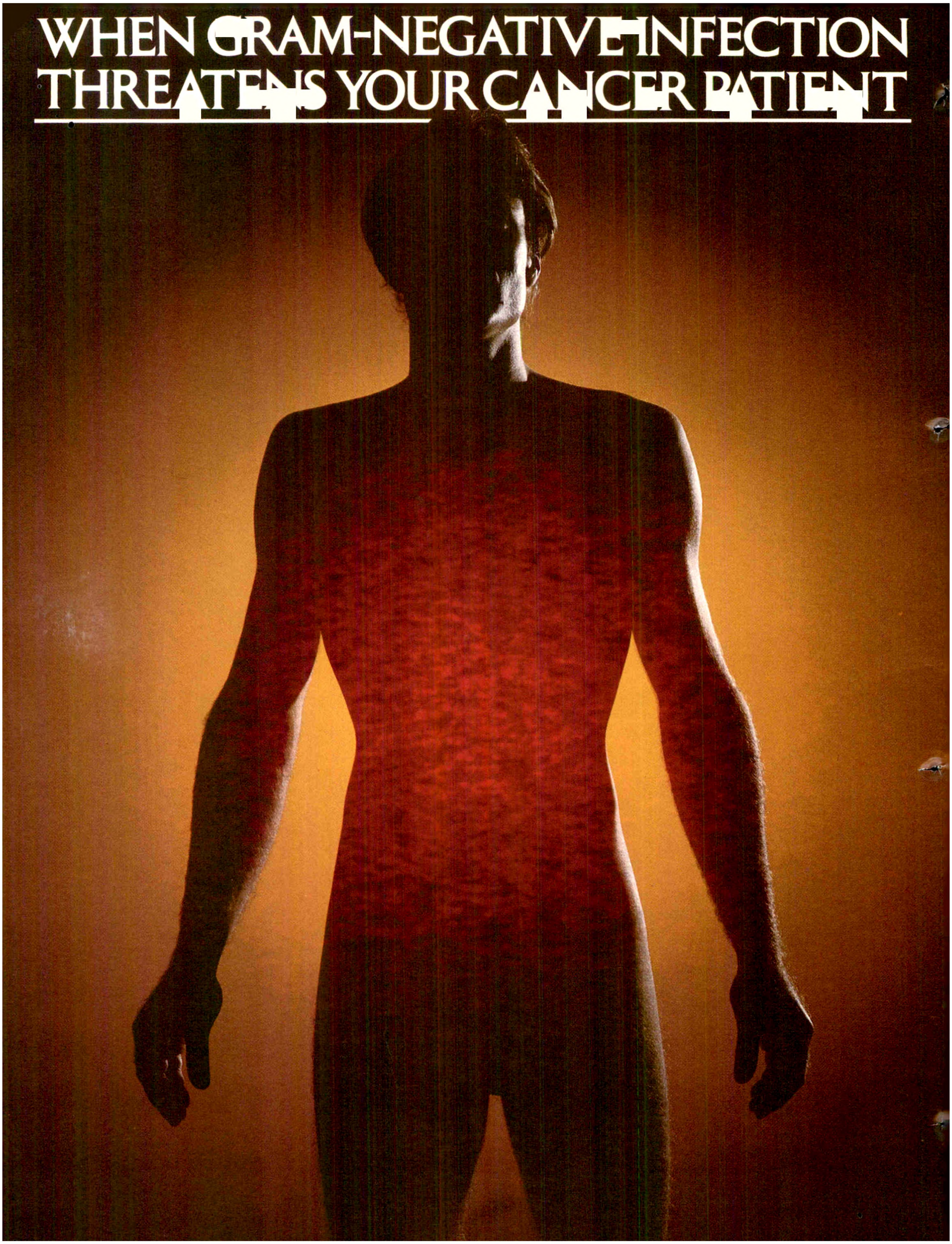
NEW DERMILITE II®

HYPO-ALLERGENIC PAPER TAPE

The paper tape that really meets your needs

☐ Gentle to skin, nonirritating and highly conformable – for maximum patient comfort
☐ Superior adhesion and twice as strong as the leading paper tape . . . greater dressing security and less tape required
☐ Preferred by 75% of nurses over the leading paper tape in multi-hospital test

Johnson & Johnson
PRODUCTS INC.
The Leader in Wound Management


WHEN GRAM-NEGATIVE INFECTION
THREATENS YOUR CANCER PATIENT

TICAR®
[Ticarcillin Disodium]

AND GENTAMICIN OR TOBRAMYCIN:

EFFECTIVE CONCOMITANT THERAPY FOR SERIOUS INFECTIONS

TICAR,® when used with an appropriate aminoglycoside, provides these additional advantages:

- BROADER ANTIBACTERIAL COVERAGE *in vitro*, when combined, than each antibiotic has alone. This enlarged spectrum includes such aerobes and anaerobes as: *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella* spp., *Staphylococcus aureus*, and *Bacteroides* spp. *(B. fragilis)*.
- PROVEN *IN VITRO* SYNERGISM that reduces the MIC's (Minimum Inhibitory Concentrations) of these antibiotics for *P. aeruginosa*.*

Note: *In vitro* susceptibility should not be translated into clinical efficacy.

- TICAR is proven "...effective regardless of the patient's neutrophil count."[1]
- Wide margin of safety common to the penicillin.

Note: A history of penicillin allergy is a contraindication.

- No nephrotoxicity or ototoxicity reported to date*
- *41% lower daily sodium load* at recommended dosages, when compared to carbenicillin for treatin severe systemic *Pseudomonas* infections*

---

*Data on file, Medical Department, Beecham Laboratories.

[1] Bodey GP, et al: Management of bacterial infections in cancer patients. Reprinted with permission from: Proceedings of the 9th International Congress of Chemotherapy, London, 1975. 1. Clinical Aspects of Infections. Available on request.

Please see important brief summary of prescribing information on next page.

Beecham
laboratories
BRISTOL, TENNESSEE 37620

TICAR*
(Sterile Ticarcillin Disodium)
for Intramuscular or Intravenous Use

For complete prescribing information, consult official package insert.

ACTIONS: Ticarcillin is bactericidal; it is not absorbed orally, therefore, it must be administered intravenously or intramuscularly.

INDICATIONS: TICAR (Ticarcillin Disodium) is indicated for the treatment of the following infections:

Bacterial septicemia†
Skin and soft-tissue infections†
Acute and chronic respiratory tract infections†‡
†caused by susceptible strains of *Pseudomonas aeruginosa*, *Proteus* species (both indole-positive and indole-negative) and *Escherichia coli*.
‡(Though clinical improvement has been shown, bacteriological cures cannot be expected in patients with chronic respiratory disease or cystic fibrosis.)
Genitourinary tract infections (complicated and uncomplicated) due to susceptible strains of *Pseudomonas aeruginosa*, *Proteus* species (both indole-positive and indole-negative), *Escherichia coli*, *Enterobacter* and *Streptococcus faecalis* (enterococcus).

Ticarcillin is also indicated in the treatment of the following infections due to susceptible anaerobic bacteria:

(1) Bacterial septicemia.
(2) Lower respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess.
(3) Intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract).
(4) Infections of the female pelvis and genital tract such as endometritis, pelvic inflammatory disease, pelvic abscess and salpingitis.
(5) Skin and soft-tissue infections.

Although Ticarcillin is primarily indicated against Gram-negative infections, its *in vitro* activity against Gram-positive organisms should be considered in treating infections caused by both Gram-negative and Gram-positive organisms.

Based on the *in vitro* synergism between Ticarcillin and gentamicin sulfate or tobramycin sulfate against certain strains of *Pseudomonas aeruginosa*, combined therapy has been successful, using full therapeutic dosages.

Culturing and susceptibility testing should be performed initially and during treatment.

CONTRAINDICATIONS: A history of allergic reaction to any of the penicillins is a contraindication.

WARNINGS: Anaphylaxis may occur, especially in patients with an allergic diathesis. Check for a history of allergy to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, the drug should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to Ticarcillin therapy. Serious anaphylactic reactions require immediate emergency treatment with epinephrine, oxygen, intravenous steroids and airway management.

Some patients receiving high doses of Ticarcillin may develop hemorrhagic manifestations associated with abnormalities of coagulation tests. Patients with renal impairment, in whom excretion of Ticarcillin is delayed, should be observed for bleeding manifestations. Such patients should be dosed strictly according to recommendations. If bleeding manifestations appear, Ticarcillin treatment should be discontinued and, if necessary, appropriate therapy instituted.

PRECAUTIONS: During prolonged treatment, periodic checking for organ system dysfunction (renal, hepatic and hematopoietic) is advisable. If overgrowth of resistant organisms occurs, the appropriate therapy should be initiated.

Since the theoretical sodium content is 5.2 milliequivalents (120 mg) per gram of Ticarcillin, electrolyte and cardiac status should be monitored carefully.

In a few patients receiving intravenous Ticarcillin, hypokalemia has been reported. Serum potassium should be measured periodically.

USAGE DURING PREGNANCY: Reproduction studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the fetus due to Ticarcillin. There are no well-controlled studies in pregnant women, but investigational experience does not include any positive evidence of adverse effects on the fetus. Although there is no clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the fetus. Ticarcillin should be used in pregnant women only when clearly needed.

ADVERSE REACTIONS: The following adverse reactions may occur: skin rashes, pruritus, urticaria, drug fever, nausea, vomiting, anemia, thrombocytopenia, leukopenia, neutropenia, eosinophilia. SGOT and SGPT elevations have been reported. Patients, especially those with impaired renal function, may experience convulsions or neuromuscular excitability when very high doses of the drug are administered.

Local reactions at the site of injection have been reported. Vein irritation and phlebitis can occur, particularly when undiluted solution is directly injected into the vein.

DOSAGE AND ADMINISTRATION: Usual adult recommended dosage in bacterial septicemia, respiratory tract infections, skin and soft-tissue infections, intra-abdominal infections and infections of the female pelvis and genital tract, is 3 grams by intravenous infusion every 3, 4 or 6 hours depending on weight and severity of infection; in uncomplicated urinary tract infections, 1 gram I.M. or direct I.V. q.i.d.; in complicated urinary tract infections, 3 grams q.i.d. by I.V. infusion.

Please consult official package insert for details on dosages for patients with renal insufficiency, children, neonates and directions for use.

Supplied:
1 Gm, 3 Gm and 6 Gm Standard Vials
3 Gm and 6 Gm Piggyback Bottles

Beecham
laboratories
BRISTOL TENNESSEE 37620

Fifth Edition

Rhoads
TEXTBOOK OF SURGERY
Principles and Practice
●
Edited by JAMES D. HARDY, M.D.
with 279 contributors

Although technically a Fifth Edition of *Surgery: Principles and Practice*, this revision is new in *title, editor, contributing authors, content, approach, and format*. It has been reorganized into three major parts: General Principles of Surgical Practice; Specific Lesions and Dysfunctions Involving Various Organs; and Parasurgical Considerations.

The approach is now problem-oriented and this outstanding volume considers virtually all current problems in surgery.

More than 270 contributors give you an enormous geographical and philosophical range in one volume. Each is well known in his field and discusses management of a specific problem. Included in each of the hundreds of topics discussed are basic features of the operation including a table of basic facts; an overview of the concept under discussion; description of specific pathological conditions; surgical history; physiology; a pathophysiological diagram and an anatomical sketch whenever feasible; many excellent illustrations of disease processes and treatment procedures; possible technical errors; safeguards; postoperative problems; and complications.

2354 Pages / 1738 Illustrations / 313 Tables
5th Edition, 1977 / One Volume Format: $38.50
Two Volume Format: $45.00

Now Available in Either One or Two Volume Form!

Lippincott
J. B. LIPPINCOTT COMPANY
East Washington Square ● Phila., Pa. 19105
In Canada: J. B. Lippincott Company of Canada Ltd.
75 Horner Avenue, Toronto, Ontario M8Z 4X7

Please send me:
Rhoads TEXTBOOK OF SURGERY
☐ 1 Vol. $38.50 ☐ 2 Vols. $45.00
Name ____________________
Address ____________________
City __________ State ______ Zip ______
☐ Payment enclosed (Save postage and handling) ☐ Charge and bill me (Plus postage and handling)
Also available at your medical bookstore. AS 8/79

UP-TO-DATE CUMULATIVE INDEX

Cancer

A Journal of the American Cancer Society, Inc.

TEN-YEAR CUMULATIVE INDEX OF SUBJECTS AND AUTHORS

VOLUMES 18–34. JANUARY 1965–DECEMBER 1974

The 10-year Cumulative Index to CANCER, printed in an easy-to-locate format is a convenient useful reference to the findings and developments in cancer as published in this official publication of The American Cancer Society during the years 1965 through 1974.

Completely cross-referenced, the key indexing words are those of the Medical Subjects Headings (MESH) of the National Library of Medicine.

In the Subject Index, under appropriate category headings set in bold face type, the complete title to each article is listed followed by author's name in parentheses, and the specific volume, page citation. Over 25,000 subject entries are included.

The Author Index, comprising some 10,000 entries, lists the principal author/s for each article and also cites volume and page location of the article.

In 328 pages, 7½ × 10¼, the outward appearance of the Cumulative Index matches that of the Journal CANCER itself. Price postpaid is $25.00 per copy. U.S., $26.00 all others.

CANCER

J. B. Lippincott Company
Attn. J. W. Bradley, Circulation Manager
East Washington Square, Philadelphia, Pa. 19105

Please send ______ copies of CANCER's Ten-Year Cumulative Index (1965–1974), at $25.00 per copy postpaid U.S. ($26.00 all others).

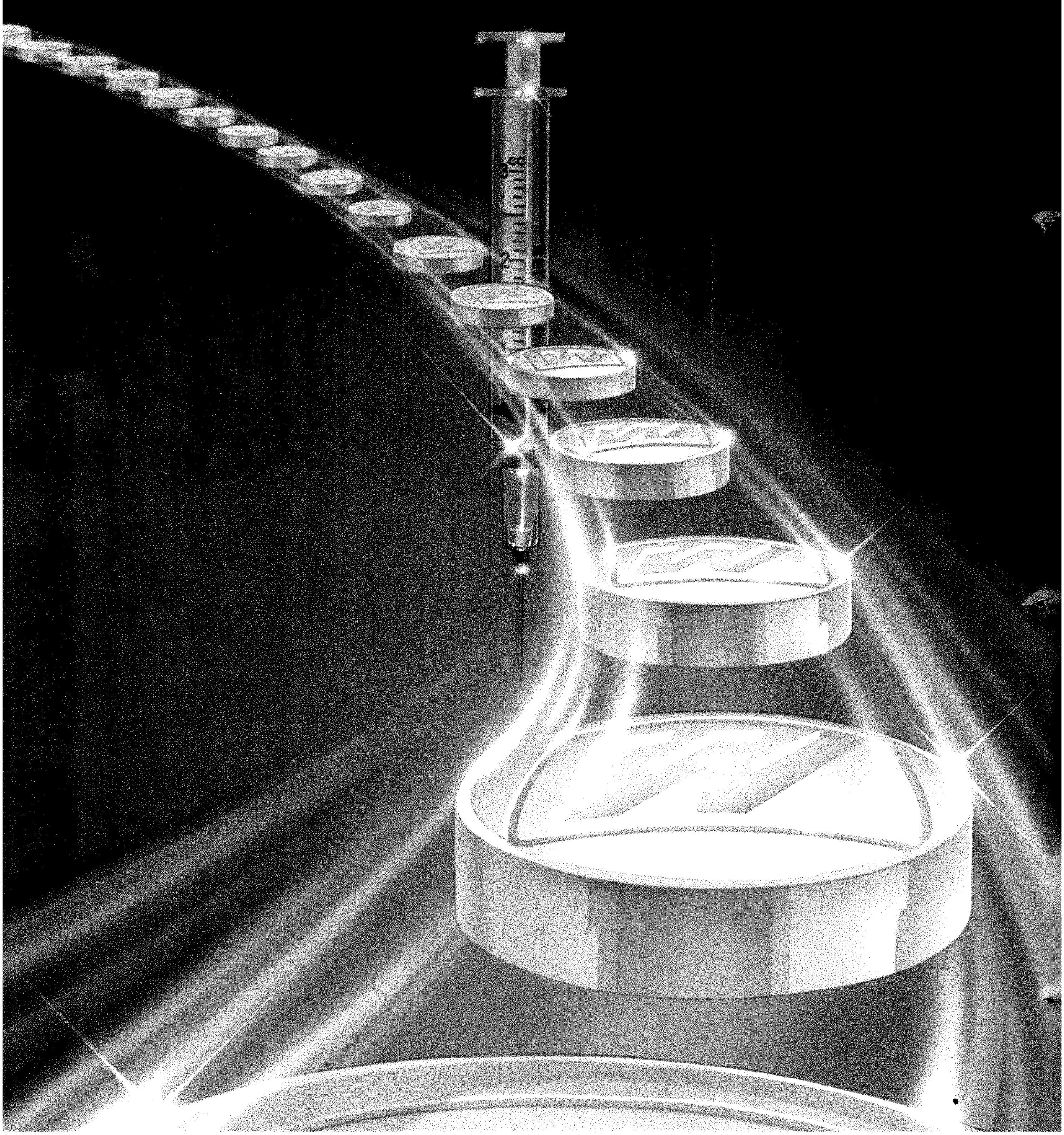
☐ Payment herewith ☐ Send Invoice

Name ______________________________
(Please Print)

Address ______________________________

City/State/Zip ______________________________

When the need for injectables is over... help keep your patient free of pain.



Potent – Dependable – Analgesic

Talwin® 50

brand of . equivalent to 50 mg base
pentazocine HCl tablets, NF (IV)

A unique agonist/antagonist.
Relieves pain as well as 60 mg of codeine.

MILD ANALGESICS OFTEN DON'T WORK

In a double-blind single dose study involving 225 adult inpatients, the comparative efficacy of 650 mg aspirin and 65 mg dextropropoxyphene, was compared to 50 mg of pentazocine for relief of postoperative pain.*

- All patients were suffering from moderate or severe pain.
- Pregnant women as well as patients with known renal, respiratory, cardiac, or hepatic insufficiency were excluded.
- The onset of action of pentazocine was rapid.
- Although aspirin, dextropropoxyphene, and pentazocine produced significant relief from pain, pentazocine was significantly more effective at a half hour.
- Side effects were recorded for 16 patients: in the aspirin group 2 patients complained of drowsiness and 1 of dizziness. In the dextropropoxyphene group 5 patients vomited and 3 patients complained of drowsiness or dizziness, while 5 patients who had received pentazocine complained of dizziness.
- Pentazocine should be an oral analgesic of choice for treatment of postoperative pain.

The advantages of Talwin 50:

The combined agonist/antagonist properties of Talwin 50 make it a drug to be considered, particularly when pain is likely to be of a persistent nature. When such pain exists, the potential for agonist dependency as well as complicating agonist side effects may be reduced by the use of Talwin 50.

Talwin 50 shows infrequent occurrence of certain adverse effects as:

- Severe respiratory depression
- Urinary retention
- Hypotension
- Tachycardia
- Constipation

While others such as nausea and dizziness are more common.

Among RARELY REPORTED REACTIONS are those of a psychiatric nature. Even the most acute CNS reactions —hallucinations (usually visual)—have cleared spontaneously within a period of hours. Withdrawal symptoms after prolonged use of Talwin 50 for the relief of pain have rarely been reported, even when administration was abruptly discontinued. There have been a few reports of dependence with orally administered Talwin 50. Patients with a history of drug dependence should be under close supervision while receiving Talwin 50 orally. See the following important product information as to dependency potential.

For Continuing Postsurgical Pain Control

Talwin® 50

brand of . equivalent to 50 mg base
pentazocine HCl tablets, NF (IV)

1 or 2 tablets every three or four hours.

*Kay B: A clinical comparison of orally administered aspirin, dextropropoxyphene and pentazocine in the treatment of postoperative pain. *J Int Med Res* 2:149-152, 1974.

See important product information including warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations, a brief summary of which follows.

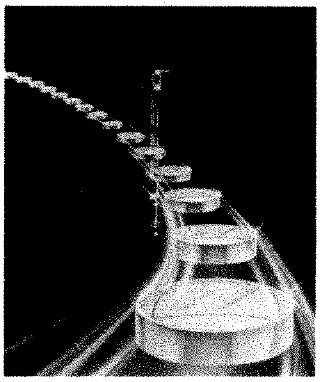
Potent—Dependable—Analgesic

Talwin® 50

brand of . equivalent to 50 mg base
pentazocine HCl tablets, NF Ⓒ IV

Relieves pain of a moderate to severe nature.

Usual initial adult dose is 1 tablet every 3 or 4 hours.



Please consult full prescribing information before prescribing. A summary follows:
TALWIN 50 is intended for the relief of moderate to severe pain. One 50 mg tablet appears equivalent in analgesic effect to 60 mg (1 gr) of codeine. TALWIN 50 is a weak narcotic antagonist with sedative activity.

Contraindication:
Hypersensitivity to pentazocine.

Warnings:
Drug Dependence. There have been instances of psychological and physical dependence on parenteral pentazocine in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral pentazocine has resulted in withdrawal symptoms. There have been a few reports of dependence and of withdrawal symptoms with orally administered TALWIN 50. Patients with a history of drug dependence should be under close supervision while receiving TALWIN 50 orally. There have been rare reports of possible abstinence syndromes in newborns after prolonged use of TALWIN 50 during pregnancy.

In prescribing TALWIN 50 for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure. TALWIN 50 may elevate cerebrospinal fluid pressure. This may be markedly exaggerated in the presence of head injury, intracranial lesions and a preexisting increase in intracranial pressure. TALWIN 50 may obscure the clinical course of patients with head injuries. TALWIN 50 should be used with extreme caution in such patients and only if its use is deemed essential.

Usage in Pregnancy. Safe use of TALWIN 50 during pregnancy (other than labor) has not been established. Although no teratogenic or embryotoxic effects have been reported in animals, TALWIN 50 should be administered to pregnant patients (other than labor) only when potential benefits outweigh possible hazards, and cautiously in labor of women delivering prematurely.

Acute CNS Manifestations. In therapeutic dosages, rarely, transient hallucinations (usually visual), disorientation, and confusion may occur. Observe such patients carefully and check vital signs. Use caution if the drug is reinstituted since the acute CNS manifestations may recur.

Usage in Children. Not presently recommended under 12.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions:
TALWIN 50 has been rarely reported to cause respiratory depression. It should be used with caution in patients with respiratory depression, severely limited respiratory reserve, bronchospasm, cyanosis, renal or hepatic dysfunction. Caution should also be used with patients prone to convulsive disorders and those about to undergo biliary surgery. As with other strong analgesics, use with caution in patients with myocardial infarction who have nausea or vomiting. Patients previously given narcotics, including methadone, may experience withdrawal symptoms after receiving TALWIN 50.

Adverse Reactions:
Reactions reported after oral administration of TALWIN 50 include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. *CNS effects:* dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations; and rarely tremor, irritability, excitement, tinnitus. *Autonomic:* sweating; infrequently flushing; and rarely chills. *Allergic:* infrequently rash; and rarely urticaria, edema of the face. *Cardiovascular:* infrequently decrease in blood pressure, tachycardia. *Hematologic:* rarely depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia. *Other:* rarely respiratory depression, urinary retention, paresthesia, toxic epidermal necrolysis.

Dosage and Administration:
Adults: The usual initial adult dose is 1 tablet (50 mg) every three or four hours. This may be increased to 2 tablets (100 mg) when needed. Total daily dosage should not exceed 600 mg. Tolerance is rare. Abrupt discontinuance following chronic use has rarely caused withdrawal symptoms.

Overdosage:
Oxygen, parenteral naloxone, intravenous fluids, vasopressors, assisted or controlled ventilation, and other supportive measures should be employed as indicated.

WNT5594

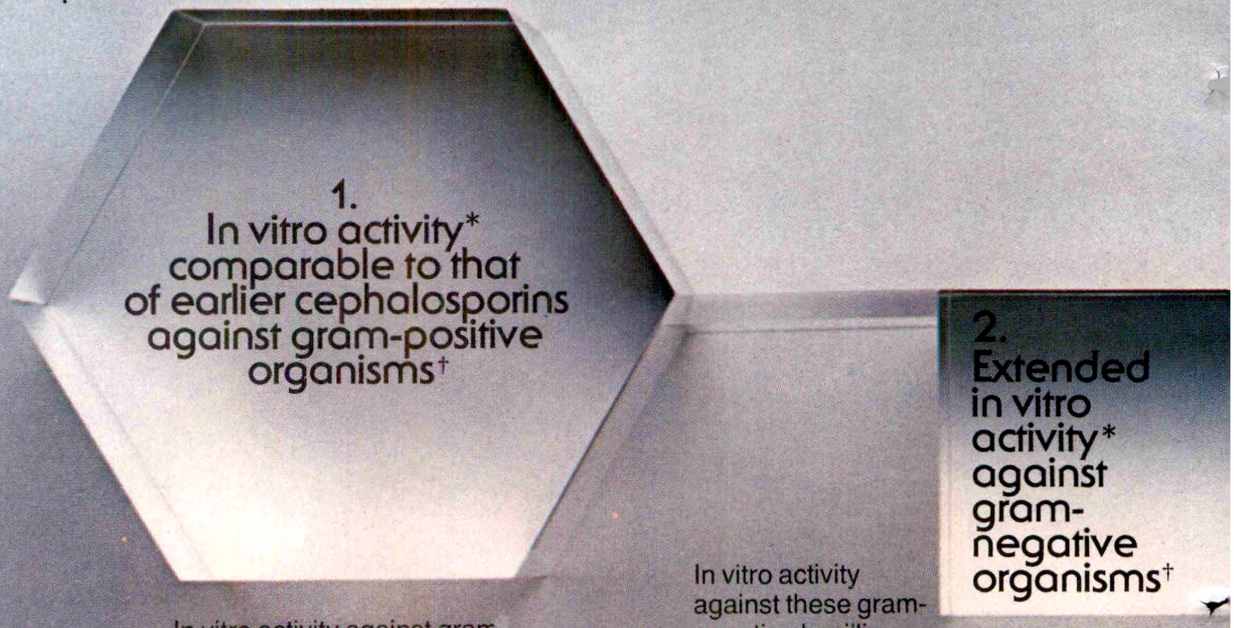
Winthrop
90 PARK AVENUE
NEW YORK N.Y. 10016

From Lilly, world leader
in cephalosporin research

A cephalosporin with
extended gram-negative
in vitro activity

1 gm* in 10 and 100-ml-size vials
*Equivalent to cefamandole activity.

Cefamandole provides



1.
In vitro activity* comparable to that of earlier cephalosporins against gram-positive organisms†

In vitro activity against gram-positive organisms comparable to that of cephalothin[1]

2.
Extended in vitro activity* against gram-negative organisms†

In vitro activity against these gram-negative bacilli: *Escherichia coli, Klebsiella pneumoniae, P. mirabilis, P. rettgeri, P. morganii, P. vulgaris,*† *Enterobacter,*† and *Haemophilus influenzae.*[2,3] Cefamandole has more in vitro potency against *Enterobacter* than do other cephalosporins.† *The cefamandole susceptibility disc is recommended for gram-negative testing.*

In vitro activity against *H. influenzae:* Among newer cephalosporins, only cefamandole has in vitro activity against *H. influenzae* which is both comparable to that of chloramphenicol and superior to that of ampicillin.[4]

MANDOL® I.M./I.V.
Cefamandole Nafate

an extension of
cephalosporin gram-negative
in vitro activity

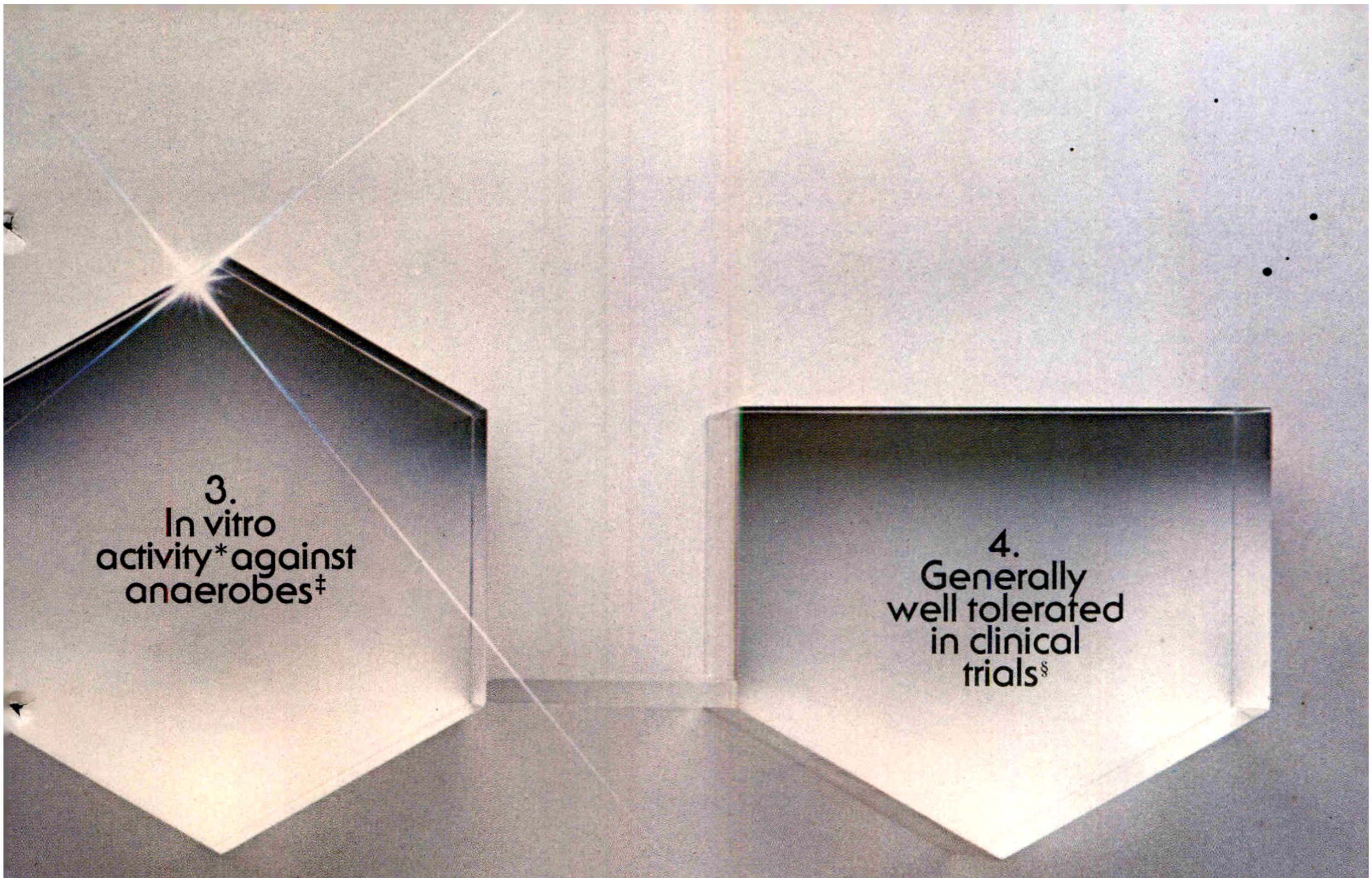
---

*In vitro activity is not necessarily indicative of clinical effectiveness.

†*Pseudomonas, Acinetobacter calcoaceticus* (formerly *Mima* and *Herellea* species), most *Serratia,* enterococci (e.g., *Streptococcus faecalis*), and some strains of *Proteus vulgaris* are resistant in in vitro tests. Initially susceptible strains of *Enterobacter* may occasionally become resistant during therapy.

See summary of prescribing information on last page for Indications.

See last page of this advertisement for summary of prescribing information.


3.
In vitro activity* against anaerobes‡
4.
Generally well tolerated in clinical trials§

In vitro activity against *Clostridium* sp., *Bacteroides* sp.,‡ and gram-positive anaerobic streptococci

*In vitro activity is not necessarily indicative of clinical effectiveness.

‡Most strains of *Bacteroides fragilis* are resistant in vitro; however, infections caused by susceptible strains have been treated successfully.

See summary of prescribing information on last page for Indications.

On the basis of clinical trial experience so far reported, cefamandole seems to be as well tolerated in therapy as the earlier cephalosporins.

§*Note:* Mandol® (cefamandole nafate, Lilly) is contraindicated in patients with known allergy to cephalosporins and should be given cautiously to penicillin-sensitive patients. (See summary of prescribing information on last page for Contraindication, Warnings, Precautions, and Adverse Reactions.)

I.M./I.V. flexibility
Cefamandole may be given both I.M. and I.V.

Indicated use with aminoglycoside
Cefamandole is indicated for use concomitantly with an aminoglycoside (see summary of prescribing information for Precautions) in certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious bacterial infections in which the causative organism has not been identified.

Recommended doses of both antibiotics may be given, depending on the severity of the infection and the patient's condition. Renal function of the patient should be carefully monitored, especially if higher dosages of the antibiotics are administered. Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

References
1. Antimicrob. Agents Chemother., *9:*994, 1976.
2. Antimicrob. Agents Chemother., *9:*452, 1976.
3. Antimicrob. Agents Chemother., *8:*679, 1975.
4. Antimicrob. Agents Chemother., *8:*91, 1975.

Lilly

900340

MANDOL® I.M./I.V.

Cefamandole Nafate

Brief Summary. Consult the package literature for prescribing information.

Indications and Usage: Mandol is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae, Klebsiella* species, *Staphylococcus aureus* (penicillinase and non-penicillinase-producing), beta-hemolytic streptococci, and *Proteus mirabilis*

Urinary tract infections caused by *Escherichia coli, Proteus* species (both indole-negative and indole-positive), *Enterobacter* species, *Klebsiella* species, group D streptococci (*Note:* Most enterococci, e.g., *S. faecalis,* are resistant), and *S. epidermidis*

Peritonitis caused by *E. coli* and *Enterobacter* species

Septicemia caused by *E. coli, S. aureus* (penicillinase and non-penicillinase-producing), *S. pneumoniae, S. pyogenes* (group A beta-hemolytic streptococci), *H. influenzae,* and *Klebsiella* species

Skin and skin-structure infections caused by *S. aureus* (penicillinase and non-penicillinase-producing), *S. pyogenes* (group A beta-hemolytic streptococci), *H. influenzae, E. coli, Enterobacter* species, and *P. mirabilis*

Clinical microbiologic studies in nongonococcal pelvic inflammatory disease in females, lower respiratory infections, and skin infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. Mandol has been used successfully in these infections in which several organisms have been isolated. Most strains of *Bacteroides fragilis* are resistant in vitro; however, infections caused by susceptible strains have been treated successfully.

Specimens for bacteriologic cultures should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefamandole. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, Mandol may be used concomitantly with an aminoglycoside (*see* Precautions). The recommended doses of both antibiotics may be given, depending on the severity of the infection and the patient's condition. The renal function of the patient should be carefully monitored, especially if higher dosages of the antibiotics are to be administered.

Antibiotic therapy of beta-hemolytic streptococcal infections should continue for at least ten days.

Contraindication: Mandol is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY WITH MANDOL IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

In newborn infants, accumulation of other cephalosporin-class antibiotics (with resulting prolongation of drug half-life) has been reported.

Precautions: Although Mandol rarely produces alteration in kidney function, evaluation of renal status is recommended, especially in seriously ill patients receiving maximum doses.

Prolonged use of Mandol may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly). There may be a false-positive test for proteinuria with acid and denaturization-precipitation tests.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Usage in Infancy—Mandol has been effectively used in this age group, but all laboratory parameters have not been extensively studied in infants between one and six months of age; safety of this product has not been established in prematures and infants under one month of age. Therefore, if Mandol is administered to infants, the physician should determine if the potential benefits outweigh the possible risks involved.

Adverse Reactions: *Hypersensitivity*—Maculopapular rash, urticaria, eosinophilia, and drug fever have been reported. These reactions are more likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—Neutropenia and thrombocytopenia have been reported rarely. Some individuals have developed positive direct Coombs tests during treatment with the cephalosporin antibiotics.

Liver—Transient rise in SGOT, SGPT, and alkaline phosphatase levels has been noted.

Kidney—Decreased creatinine clearance has been reported in patients with prior renal impairment. As with some other cephalosporins, transitory elevations of BUN have occasionally been observed with Mandol; their frequency increases in patients over 50 years of age. In some of these cases, there was also a mild increase in serum creatinine.

Local Reactions—Pain on intramuscular injection is infrequent. Thrombophlebitis occurs rarely.

Administration and Dosage: *Dosage—Adults:* The usual dosage range for cefamandole is 500 mg to 1 gm every four to eight hours.

In infections of skin structures and in uncomplicated pneumonia, a dosage of 500 mg every six hours is adequate.

In uncomplicated urinary tract infections, a dosage of 500 mg every eight hours is sufficient. In more serious urinary tract infections, a dosage of 1 gm every eight hours may be needed.

In severe infections, 1-gm doses may be given at four to six-hour intervals.

In life-threatening infections or infections due to less susceptible organisms, doses up to 2 gm every four hours (i.e., 12 gm per day) may be needed.

Infants and Children: Administration of 50 to 100 mg/kg/day in equally divided doses every four to eight hours has been effective for most infections susceptible to Mandol. This may be increased to a total daily dose of 150 mg/kg (not to exceed the maximum adult dose) for severe infections. (*See* Warnings and Precautions for this age group.)

Note: As with antibiotic therapy in general, administration of Mandol should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or after evidence of bacterial eradication has been obtained; a minimum of ten days of treatment is recommended in infections caused by group A beta-hemolytic streptococci in order to guard against the risk of rheumatic fever or glomerulonephritis; frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infection and may be required for several months after therapy has been completed; persistent infections may require treatment for several weeks; and doses smaller than those indicated above should not be used.

Impaired Renal Function—When renal function is impaired, a reduced dosage must be employed and the serum levels closely monitored. After an initial dose of 1 to 2 gm (depending on the severity of infection), a maintenance dosage schedule should be followed (see chart). Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organism.

MAINTENANCE DOSAGE GUIDE
FOR PATIENTS WITH RENAL IMPAIRMENT

Creatinine Clearance (ml/min/1.73 m²)	Renal Function	Life-Threatening Infections—Maximum Dosage	Less Severe Infections
>80	Normal	2 gm q 4 h	1-2 gm q 6 h
80-50	Mild Impairment	1.5 gm q 4 h OR 2 gm q 6 h	0.75-1.5 gm q 6 h
50-25	Moderate Impairment	1.5 gm q 6 h OR 2 gm q 8 h	0.75-1.5 gm q 8 h
25-10	Severe Impairment	1 gm q 6 h OR 1.25 gm q 8 h	0.5-1 gm q 8 h
10-2	Marked Impairment	0.67 gm q 8 h OR 1 gm q 12 h	0.5-0.75 gm q 12 h
<2	None	0.5 gm q 8 h OR 0.75 gm q 12 h	0.25-0.5 gm q 12 h

When only serum creatinine is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$\text{Males: } \frac{\text{Weight (kg)} \times (146-\text{age})}{72 \times \text{serum creatinine}}$$

$$\text{Females: } 0.9 \times \text{above value}$$

How Supplied: Vials Mandol® (cefamandole nafate, Lilly), for Injection, 500 mg and 1 gm (equivalent to cefamandole activity), 10-ml size, in packages of 1 and Traypaks™ (multivial cartons, Lilly) of 25; 2 gm (equivalent to cefamandole activity), 20-ml size, in packages of 1 and Traypaks of 10; 1 and 2 gm (equivalent to cefamandole activity), 100-ml size, in Traypaks of 10. [101378]

Lilly

Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

900340

A Method for Primary Reconstruction Following Radical Excision of Sacrococcygeal Pilonidal Disease

RONALD H. FISHBEIN, JACOB C. HANDELSMAN

From The Departments of Surgery, The Sinai Hospital and the Johns Hopkins University School of Medicine, Baltimore, Maryland

A great variety of procedures have been proposed for the cure of Sacrococcygeal pilonidal disease. Initial enthusiasm has usually given way to disappointment when it is realized that the treatment is painful, the hospitalization is prolonged, the aftercare is tedious or the original condition appears to have recurred. A technique is described which permits the total extirpation of cyst and sinus tracts while allowing for a tensionless wound closure by advancement of a buttock flap. Hospitalization is brief and the postoperative course is comfortable. Fifty such operations have been performed since November 1968. In the first group of thirty patients operated upon between three and ten years ago, a single bonafide failure occurred. An additional twenty patients have been successfully treated for an overall failure rate of 2%.

THE HISTORY OF THE TREATMENT of sacrococcygeal pilonidal disease has been noteworthy for the variety and dissimilarity of the proposed therapies. Thermal[19] or cryo[8] destruction of the sinus tracts, local irradiation,[26,28] injection of sclerosing agents or irritants such as phenol,[2,3,16,27] incision and packing,[10] excision and packing,[7] excision and partial closure,[23] unroofing and saucerization or "marsupialization",[1,5] excision with primary closure,[13,21,25] excision with closure by z-plasty,[17,18] excision with closure by rotation flap[6,11,15] have all been proposed. The results have generally been less than satisfactory and the reported recurrence rates have too often been unacceptable.

The vast majority of those individuals afflicted with pilonidal disease of the sacrococcygeal region belong to the 15–30-year-old age group, hence an enormous amount of time may be lost from school and employment as a result of the natural history of the disease and its treatment. Consequently, the economic loss is incalculable. The social restrictions, embarrassment and chronic discomfort incurred by this disorder can scarcely be appreciated.

The lack of agreement concerning the proper treatment of this affliction reflects, in part, the lack of understanding regarding its etiology. The concept of a developmental anomaly[12] has been slow to dispel.[22] Direct local trauma,[24] impalement by broken hair shafts,[4,20] stretching of the internatal skin with the production of giant pores,[14] trichofolliculitis and generally ineffective personal hygiene with skin maceration have all been implicated in the causation of pilonidal disease of the sacrococcygeal area.

Hence, we are dealing with a poorly understood disease which has a propensity for disrupting the lives of young people and for which we have an assortment of therapeutic maneuvers. Some of these operations or treatments cause considerable discomfort, some require strict curtailment of bowel function and physical activity, some necessitate inordinately prolonged periods of wound care and dressing changes, and most culminate in distressingly high failure rates.[21]

It would seem then that a procedure which is not uncomfortable, results in a closed wound which heals per primum, requires minimal restriction of activity and which carries with it a favorable cure rate would be ideal.

Two of the most promising surgical approaches to the permanent cure of this disorder have been the total excision of the cyst and sinus with closure of the resultant wound by either z-plasty[17,18] or the use of a local rotation flap.[6,11,15] Excellent initial healing as well as enviable long-term cures have been claimed.

This report describes an operation performed upon a modest number of patients either as a primary procedure or as a secondary attempt at cure after one or more prior failures. There follows an analysis of the results and a discussion of the circumstances which appear to favor rapid recovery and long term cure. This operation was always performed electively, either during a quiescent phase or when the pilonidal cyst and sinus tract was grossly septic and draining. It has

---

Reprint requests: Ronald H. Fishbein, M.D., 220 West Cold Spring Lane, Baltimore, Maryland 21210.

Submitted for publication: March 22, 1979.

0003-4932/79/0800/0231 $00.75 © J. B. Lippincott Company

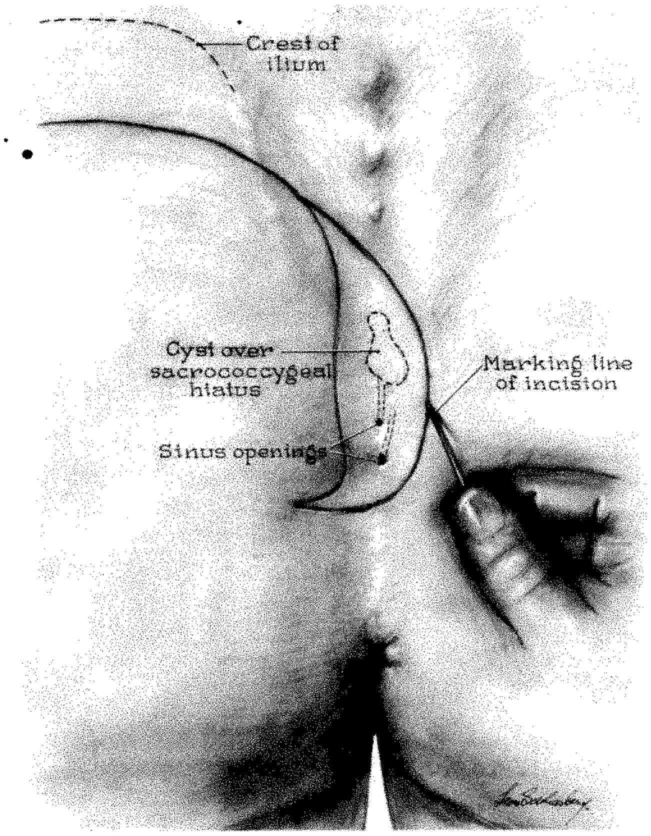


FIG. 1. The proposed line of incision includes the orifices of the sinus tracts and the cyst cavity. A curvilinear extension superiorly completes the design of a rotation flap.

never been performed in the presence of an acute pilonidal abscess.

Operative Technique

Under general or spinal anesthetic, the patient is placed in the prone position with hips slightly flexed. The buttocks are neither spread apart nor taped. After meticulous shaving and skin preparation, a patent tract may be probed and injected with methylene blue in hydrogen peroxide. Using a sterile skin-marking pen, a crescentic outline is traced. The crescent may face left or right but should include what is anticipated to be the margins of the cyst cavity and all of the ostia associated with the sinus tract (Fig. 1). When the cavity lies to one side of the midline it is best to develop the flap from the opposite buttock. The lower end of the crescent is intentionally carried across the midline and on to the opposite buttock. Until quite recently, the excision of the cyst and sinus was accomplished using a conventional vertically oriented ellipse. However carefully the wounds were coapted the most caudal extent would tend to invert. The crescentic excision eliminates this hazard by crossing the natal crease transversely. The excision is then performed using a scalpel for the skin and an electrocutting-cautery for the remaining deeper layers of the wound (Fig. 2a). The excision may be broadened should the extent of the dye-stained cavity prove to be greater than anticipated. It is important though that the walls of the operative defect remain perpendicular. This may require the excision of additional skin beyond the outline of the original crescent. The depth of excision is limited to the level of the postsacral fascia. With the block of skin and diseased tissue removed from the field, a curvilinear incision is performed from the cranial end of the defect across the upper pole of the buttock as a continuation of the crescentic arc (Fig. 2b). This incision is deepened to traverse the thick dermal and subcutaneous layers as well as the thin but sinewy fascial envelope of the gluteus maximus muscle. With the aid of the cutting cautery, the subfascial plane is followed, gradually elevating the full thickness flap while exposing the bare fibers of the muscle (Figs. 3a and b). The flap thus is composed of skin, subcutis and gluteal fascia. The distance to which the flap is elevated, relates directly to the extent of the defect produced by the excision of the cyst. The vascular integrity of the flap has never been a matter of concern since the length to width ratio rarely approaches even 1.5. It is at this time that the previously applied saline-moistened packs protecting the wound edges are removed and meticulous hemostasis achieved.

Two multiple-hole wound catheters are introduced through separate stab incisions several centimeters above and on the same side as the flap (Fig. 4a). A portable suction apparatus will eventually be connected to the catheters.

If the flap has been developed sufficiently, little or no effort will be required to draw it medially and caudally and to bring the tip to meet the opposite wall of the defect. Rotation of the flap rarely produces a significant disparity in the thickness of the opposing walls of the wound. The elasticity and spongy compressibility of these tissues makes them forgiving when compensating for discrepancies in height and length.

Heavy-weight absorbable suture material is used to approximate the fascia as well as the fibro-fatty subcutis (Figs. 4b and c). Lighter but similar suture material brings the dermal layer together. Finally a series of monofilament nylon or polypropylene vertical mattress sutures are placed across the superficial skin edges (Figs. 5a–c). The wound catheters are kept on suction for three to four days and then removed, and the patient discharged.

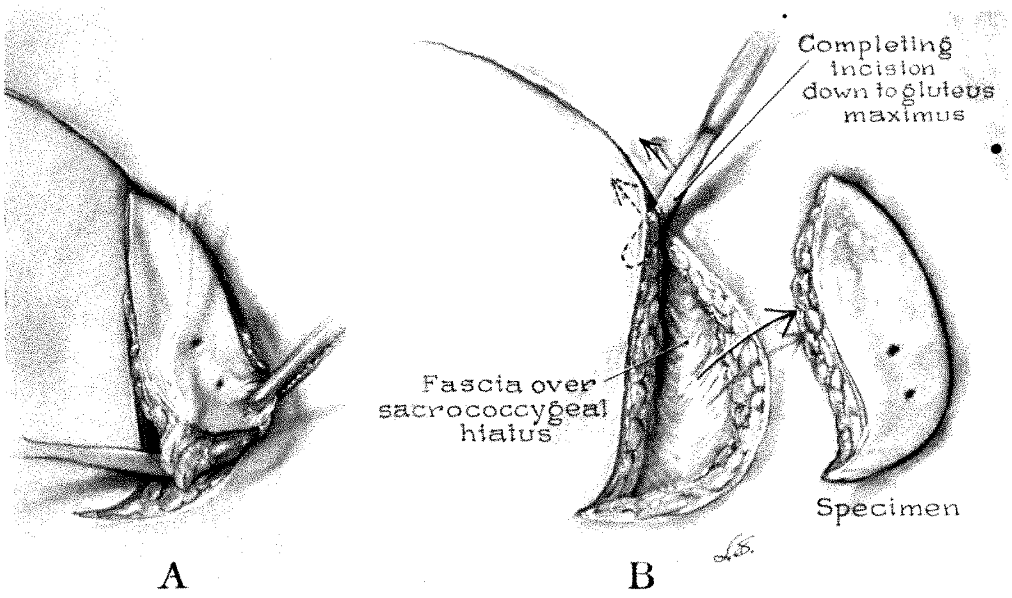

Completing incision down to gluteus maximus
Fascia over sacrococcygeal hiatus
Specimen
A
B

FIG. 2. The specimen is removed, exposing the musculo-fascial origins of the paired gluteus maximus muscles and the sacrococcygeal ligament.

Postoperative Care

From the first moment that it is considered prudent to do so, following the general or spinal anesthetic, the patient is encouraged to stand, sit or walk. A normal diet is provided and no attempt is made to restrict bowel evacuation. Though analgesics are available, rarely, if ever, has any been requested beyond the first 24 hours. The initial adhesive tape dressing placed across the buttocks is either removed and replaced with a similar dressing at the time of discharge or, where preferred by the patient, no dressing is used and support is achieved with an elastic abdominal binder worn low across the hips. This latter method allows the patient to bathe or shower during the interval between discharge and when the skin sutures are removed on the tenth to

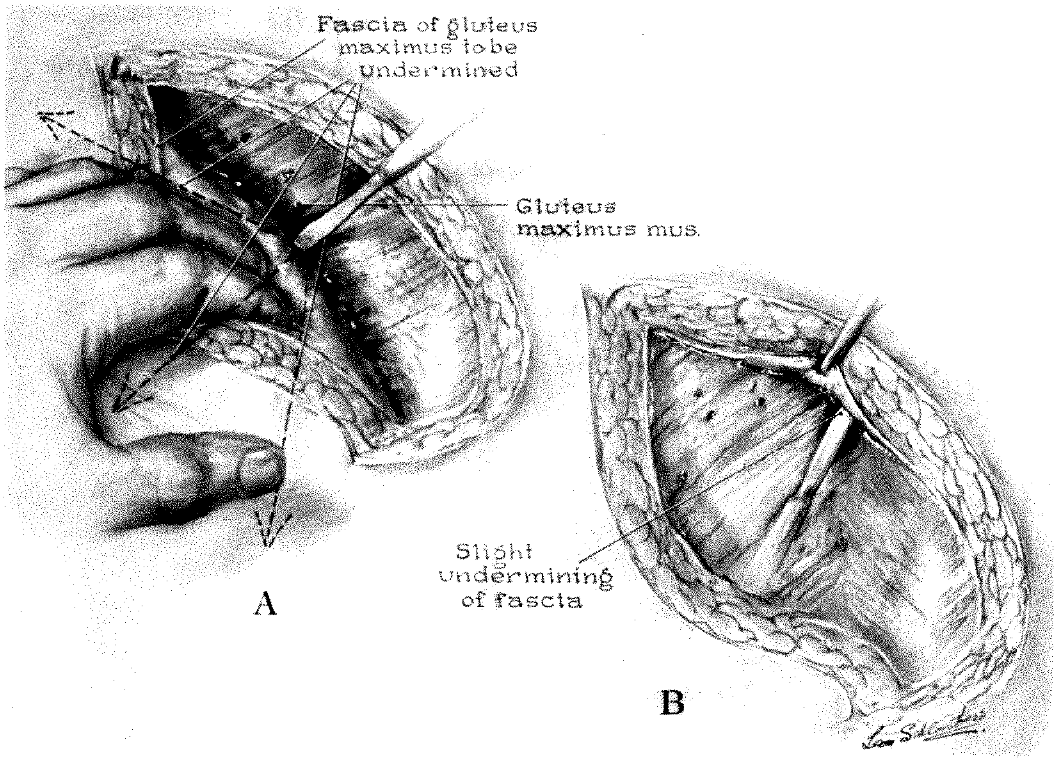

Fascia of gluteus maximus to be undermined
Gluteus maximus mus.
Slight undermining of fascia
A
B

FIG. 3. Stages in the subfascial development of the buttock flap exposing bare fibers of the gluteus maximus muscle.

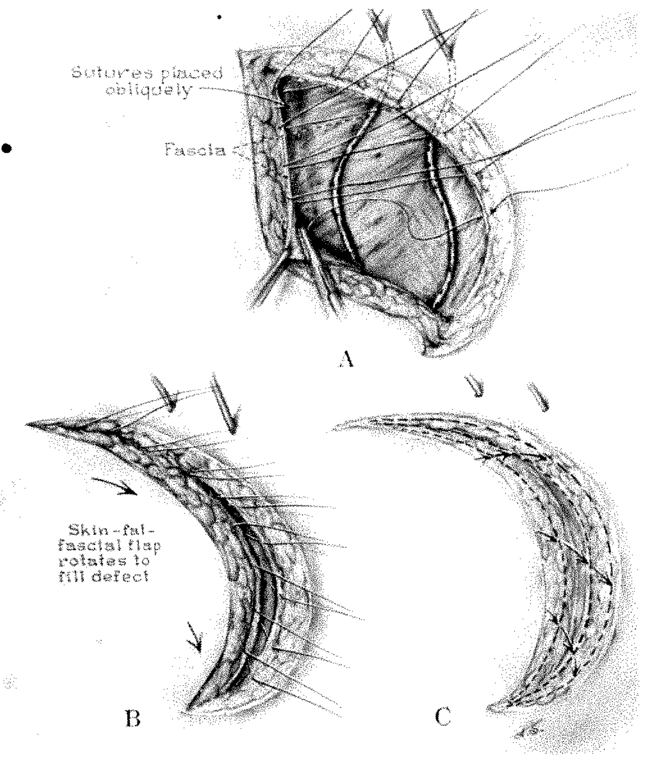


FIG. 4. Stages in the advancement and rotation of the buttock flap to fill the defect left by the primary excision.

twelfth postoperative day. Only those activities which place the patient in jeopardy of falling directly on the operative site are discouraged for the first several weeks.

Results

Fifty patients have been operated upon using this technique since November, 1968. Thirty were male, twenty female. Thirty patients were operated upon during the period of November, 1968 thru November, 1975 (Group I). Twenty were operated upon after November, 1975 (Group II). Over three years has elapsed since the last patient in Group I was treated. One bonafide failure occurred in a young man who did not benefit from even a second rotation flap. One patient in Group I as well as two patients in Group II experienced minor healing problems which required diminutive corrections. Two healing deficiencies may be ascribed to the use of a vertical elliptical excision resulting in improper coaptation of the wound edges at the lower most point of the wound. The third patient required a minor revision as a result of the failure of the wound catheters to adequately evacuate the operative seroma. As a result, an infected seroma necessitated through the wound approximately two weeks postoperatively. A very superficial tract with skin bridge required local excision.

After ten years of experience with this operation only one known failure in 50 cases has occurred (2%).

Discussion

Although no unassailable hypothesis has been established with respect to the etiology of pilonidal disease, a theory based upon the notion that it is an acquired condition seems most reasonable. Whether large skin pores, infected hair follicles, local trauma or self-impalement upon hair shafts in some combination with poor local hygiene is most often responsible, can be debated. Monro and McDermott[18] emphasized the importance of altering the local anatomy of the intergluteal cleft, while excising the granulation tissue-lined cavity and tract. A z-plasty, they reasoned, would fill out and flatten the natal crease and direct growing hair away from the midline. In addition, the obliteration of the crease should minimize friction and reduce the accumulation of detritus. To a certain extent this objective is achieved. The z-plasty effectively flattens the upper portion of the crease at the expense of the immediate postanal region, which is left unchanged.

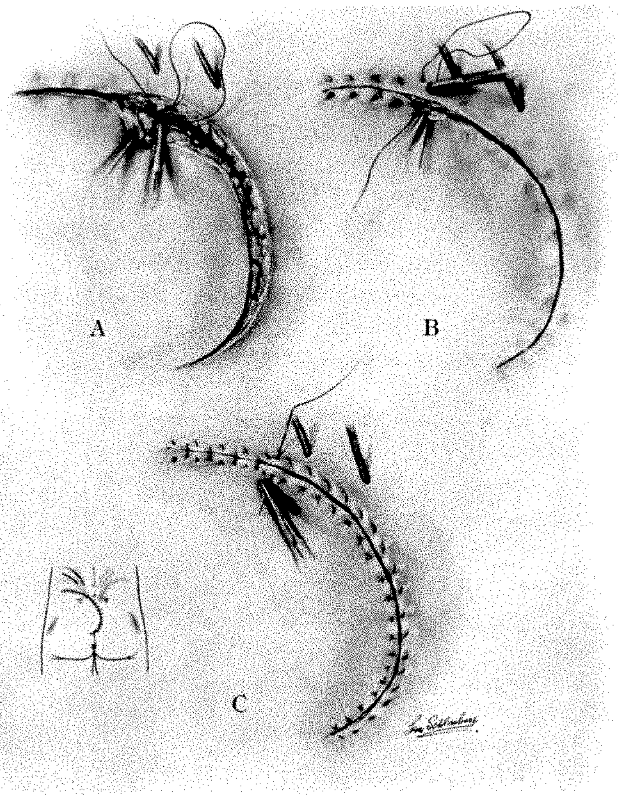


FIG. 5. The completion of the tension-less closure of the wound.

Hair shafts are directed away from the midline. Hirshowitz, et al.[11] described the fashioning of a rectangular buttock flap based inferiorly. They attached no importance to the obliteration of the natal crease and viewed the rectangular flap simply as a means of closing a large defect under minimal tension. Because they chose to raise the flap on the same side as the major portion of the excision, closure of the wound resulted in retention of the entire cleft.

The objectives of the presently described operative as well as postoperative management are derived in part from the experiences with the z-plasty and the rectangular flap. By elevating the flap on the side opposite to where the preponderance of the cyst and sinus tract is located, the rotation of the flap across the midline produces a gentle flattening of the intergluteal cleft. This is particularly important in those individuals with extremely deep clefts. It reduces friction and moisture accumulation and makes care and cleaning of the area simpler. In addition, bringing the flap across the midline eliminates the creation of a fixed scar along the midline which the rectangular flap intentionally produces.

It also seems logical to conclude that postoperative pain and the need for restriction of physical activity are related to the tension under which a wound is closed. Typical of the postoperative restriction necessitated by simple excision and primary closure is the procedure as described by Goligher.[9] Bedrest is required for nine to ten days after operation. During this time the patient is generally prompted to lay on either side for comfort while efforts are made to prevent bowel evacuation for 6 to 7 days. Hospitalization is usually necessary for 14 days. A great deal of analgesia is required when excision with primary closure is supported by the use of retention sutures. Either a z-plasty or rotation flap will allow for closure under negligible tension. Analgesics are almost entirely unnecessary following a tension-less closure.

It is also proposed that late "recurrences" after what has appeared to be an initially successful healing of the wound edges in primary excisions with simple closure are due to early, unrecognized dehiscence of the deep subcutaneous layer. This phenomenon leads to the development of a chronic subcutaneous cavity which eventually erupts through the skin, appearing not unlike the original pilonidal cyst and sinus.

An operative procedure has been proposed which allows for the radical excision of a chronic pilonidal cyst and sinus. The operation may be performed simply and rapidly. The wound is closed by a time-honored technique which eliminates tension in the tissues. As a result, the patient is provided with a brief and comfortable postoperative course. Restriction of activities is negligible. The wounds generally heal uneventfully and thus far late recurrences do not exceed 2%.

References

1. Abramson, W. J.: Simple Marsupialization Technique for Treatment of Pilonidal Sinus. Ann. Surg., 151:261, 1950.
2. Biegeleisen, H. I.: Sclerotherapy for Pilonidal Cysts. Am. J. Surg., 44:622, 1939.
3. Block, L. H. and Greene, B. L.: Pilonidal Cysts—Sclerosing Method of Treatment. Arch. Surg., 37:112, 1938.
4. Brearley, R.: Pilonidal Sinus—A New Theory of Origin. Br. J. Surg., 43:62, 1955.
5. Buie, L. A.: Practical Proctology. Philadelphia, W. B. Saunders, 1937.
6. Davies, L. S. and Starr, K. W.: Infected Pilonidal Sinus. Surg. Gynecol. Obstet., 81:309, 1945.
7. Gabriel, W. B.: The Principles and Practice of Rectal Surgery. Third edition. London: Lewis, 1948.
8. Gage, A. A. and Dutta, P.: Cryosurgery for Pilonidal Disease. Am. J. Surg., 133:249, 1977.
9. Goligher, J. C.: Surgery of the Anus, Rectum and Colon. Third Edition. Springfield, Charles C Thomas, 1975. pp. 256–276.
10. Goodsall, D. H. and Miles, W. E.: Diseases of the Anus and Rectum. London, Longmans, Green & Co.
11. Hirshowitz, B., Mahler, D. and Kaufmann-Friedmann, K.: Treatment of Pilonidal Sinus. Surg. Gynecol. Obstet., 131: 119, 1970.
12. Hodges, R. M.: Pilonidal Sinus. Boston Med. Surg. J., 103:465, 544, 1880.
13. Holm, J. and Hulten, L.: Simple Primary Closure for Pilonidal Disease. Acta Chir. Scand., 136:537, 1970.
14. Hueston, J. T.: The Aetiology of Pilonidal Sinuses. Br. J. Surg., 41:307–311, 1953.
15. Lalor, T. J.: The Plastic Flap in Closure of the Pilonidal Cyst Excision Defect. J. Int. Coll. Surg., 22:181, 1954.
16. Maurice, B. A. and Greenwood, R. K.: A Conservative Treatment of Pilonidal Sinus. Br. J. Surg., 51:510, 1964.
17. Middleton, M. D.: Treatment of Pilonidal Sinus by Z-plasty. Br. J. Surg., 55:516, 1968.
18. Monro, R. S. and McDermott, F. T.: The Elimination of Casual Factors in Pilonidal Sinus Treated by Z-plasty. Br. J. Surg., 52:177, 1965.
19. Moore, A.: Use of Diathermy Loop in Excision of Pilonidal Sinus. Aust. N. Z. J. Surg., 8:186, 1938.
20. Page, B. H.: The Entry of Hair into a Pilonidal Sinus. Br. J. Surg., 56:32, 1969.
21. Palumbo, L. T., Larimore, O. M., and Katz, I. A.: Pilonidal Cysts and Sinuses; A Statistical Review. Arch. Surg., 63: 852, 1951.
22. Patey, D. H. and Scarff, R. W.: Pathology of Postanal Pilonidal Sinus: Its bearing on Treatment. Lancet, 2:484, 1946.
23. Pearce, A. E.: Pilonidal Cystectomy with Partial Closure and Packing. Am. J. Protocol., 18:34, 1967.
24. Raffman, R.: A Re-evaluation of the Pathogenesis of Pilonidal Sinus. Ann. Surg., 150:895, 1959.
25. Rains, A. J.: Treatment of Pilonidal Sinus by Excision and Primary Closure. Br. Med. J., 5145:171, 1959.
26. Smith, R. M.: Roentgen Irradiation as an Adjunct to Surgical Treatment of Pilonidal Cyst. Am. J. Roentgenol., 38:308, 1937.
27. Stephens, F. O. and Sloane, D. R.: Conservative Management of Pilonidal Sinus. Surg. Gynecol. Obstet. 129:786, 1969.
28. Turell, R.: Radiation Therapy for Recurrent Sacrococcygeal Cysts and Sinuses. Surgery, 8:469, 1940.

Effects of Methylprednisolone on Experimental Pulmonary Injury

F. W. CHENEY, JR., M.D.,* T. H. HUANG, M.D., PH.D.,† R. GRONKA, B.S.‡

We studied the effects of methylprednisolone on pulmonary function of unanesthetized dogs with oleic acid induced pulmonary edema observed over a four day period. Methylprednisolone (30 mg/kg) was administered to 11 dogs three and 24 hours after pulmonary injury. Eleven animals were untreated after pulmonary injury and served as controls. There was no difference between the two groups until 72 hours after injury, when the venous admixture of the steroid treated animals was 11 ± 3% (SD) compared to 22 ± 8% ($p < 0.001$) in the untreated with respective Pa_{O_2} values of 76 ± 6 torr and 64 ± 8 torr ($p < 0.001$). Light microscopic examination of the lungs 96 hours after injury revealed a marked proliferation of Type II pneumocytes in the methylprednisolone treated animals. We concude that, in the oleic acid or fat embolism model of pulmonary injury, methylprednisolone significantly increases resolution of the pulmonary injury presumably by stimulation of active proliferation and maturation of Type II pneumocytes.

*From the Departments of Anesthesiology and Pathology,
University of Washington School of Medicine,
Seattle, Washington*

OLEIC ACID PRODUCES a pathophysiologic picture similar to that seen in the clinical syndrome of fat embolism,[1,10] which is one of the syndromes included in the human adult respiratory distress syndrome. The major features of this syndrome are hypoxemia, decreased lung compliance, and noncardiogenic pulmonary edema. Corticosteroids improve survival when administered prior to or after oleic acid pulmonary embolism in dogs[3,8] and rats.[19] As evidence is lacking that survival is due to improved pulmonary function, we studied the effects of methylprednisolone (Solu-Medrol) on the course of pulmonary injury from a sublethal dose of oleic acid.

Methods

Twenty-two mongrel dogs (mean weight 25 ± 3 kg SD) were anesthetized with 30 mg/kg of pentobarbital and, under sterile conditions, instrumented with triple lumen Swan-Ganz catheters and arterial lines. The Swan-Ganz catheters were placed via the external jugular vein and the arterial lines were placed in the forepaw. The distal tip of the pulmonary artery catheter was placed in the proximal pulmonary artery to avoid mixed venous blood sampling error[15] and as a result, we were unable to make pulmonary artery wedge pressure measurements in most animals. The catheters were filled with heparin and secured with dressings so that the animals could not dislodge them. Penicillin (600,000 units) and streptomycin (0.5 g) were administered intramuscularly and the animals allowed to recover for 48 hours. No further antibiotics were administered. The animals were brought to the laboratory and control measurements of arterial and mixed venous blood gases, Hgb, vascular pressures, heart rate, and cardiac output ($\dot{Q}t$) were done in unanesthetized state. USP oleic acid 0.06 ml/kg was then injected into the right atrium via the indwelling Swan-Ganz catheter. During injection of oleic acid, the animals did not show any obvious signs of discomfort except for occasional coughing. Measurements were repeated at two, four, 24, 48, 72, and 96 hours after the oleic acid injection.

The animals were divided into two groups: 1) 11 control dogs were untreated, 2) 11 steroid treated dogs received 30 mg/kg methylprednisolone intravenously three hours after oleic acid injection and again at 24 hours. After the 96 hour measurements, the animals were anesthetized with 30 mgm/kg pentobarbital, thoracotomy was performed, and the animals sacrificed by ligation of the main pulmonary artery. Samples for light microscopic examination were taken from both grossly normal and abnormal areas of the lung. The pulmonary veins were ligated at the hilum, the lungs removed and weighed. The right lung was weighed, 1 ml

---

* Professor, Department of Anesthesiology.

† Assistant Professor, Department of Pathology.

‡ Research Technologist, Department of Anesthesiology.

Reprint requests: Frederick W. Cheney, M.D., Professor, Department of Anesthesiology RN-10, University of Washington School of Medicine, Seattle, Washington 98195.

Submitted for publication: September 8, 1978.

Supported by PHS grant #HL 20612 and the Upjohn Company, Kalamazoo, Michigan.

0003-4932/79/0800/0236 $00.85 © J. B. Lippincott Company

of distilled water was added for each gram of lung weight, and the mixture homogenized in a blender. Hemoglobin of the mixture was measured. Weighed aliquots were heated at 80° in a vacuum oven for five days until weights on successive days were within 2–3% of each other. The final lung water/dry lung weight ratio was corrected for blood content of the lung. Histologic specimens were processed, embedded in paraffin, sections cut at 6 μm and stained with hematoxylin and eosin stains. Slides were then coded so that the pathologist was unaware of the treatment group to which the animal belonged. Cellular proliferation in the microscopic sections was scored according to the following criteria:

−	no proliferation
+	occasional plump cuboidal epithelial cells at the periphery of the necrotic areas
2+	Focal clusters of proliferating epithelial cells which do not form a continuous rim.
3+	A continuous rim of proliferating epithelial cells, less than 3 cells in width surrounding the periphery of the necrotic area
4+	A continuous rim of proliferating epithelial cells more than 3 cells in width surrounding the edge of the necrotic area

The entire experiment was carried out with the animals breathing room air and awake or lightly sedated with 5–10 mg/kg thiamylal. If the animals dislodged one of the intravascular catheters, a new one was rapidly inserted with the animal sedated. Cardiac output was measured by the thermal dilution technique. Venous admixture ($\dot{Q}_{VA}/\dot{Q}t$) was measured during room air breathing and calculated using the standard shunt equation.[4] Arterial and mixed venous oxygen contents were calculated using the measured hemoglobin and hemoglobin saturation which was derived from blood gas values using a computer program developed by Ruiz et al.[14] Statistical analysis was performed using the Student's unpaired t-test for comparisons between treated and untreated animals and the paired t-test for comparisons before and after oleic acid injection in each group.

Results

All 22 animals survived the 96 hour study period. In both groups, $\dot{Q}_{VA}/\dot{Q}t$ increased (Fig. 1) and Pao_2 decreased (Fig. 2) two hours after oleic acid injection as compared to control measurements. These changes persisted at about the same level for 48 hours in the steroid treated group and 72 hours in the untreated group. The major difference between groups was marked improvement in $\dot{Q}_{VA}/\dot{Q}t$ (Fig. 1) and Pao_2 (Fig. 2) at 72 hours in the treated animals. At 96 hours the $\dot{Q}_{VA}/\dot{Q}t$ of the untreated animals began to return toward pre-oleic acid levels although $\dot{Q}_{VA}/\dot{Q}t$ was still significantly higher in the untreated animals at 96 hours as compared to the treated (Fig. 1). Administration of steroids three and 24 hours after lung injury had no immediate major effect on gas exchange. Venous admixture did not decrease significantly one hour following methylprednisolone compared to $\dot{Q}_{VA}/\dot{Q}t$ measured prior to drug administration (Fig. 3). There was, however, a small but significant increase in Pao_2 without a significant change in Pa_{CO_2} one hour after the second administration of steroids (Fig. 4). Cardiac output de-

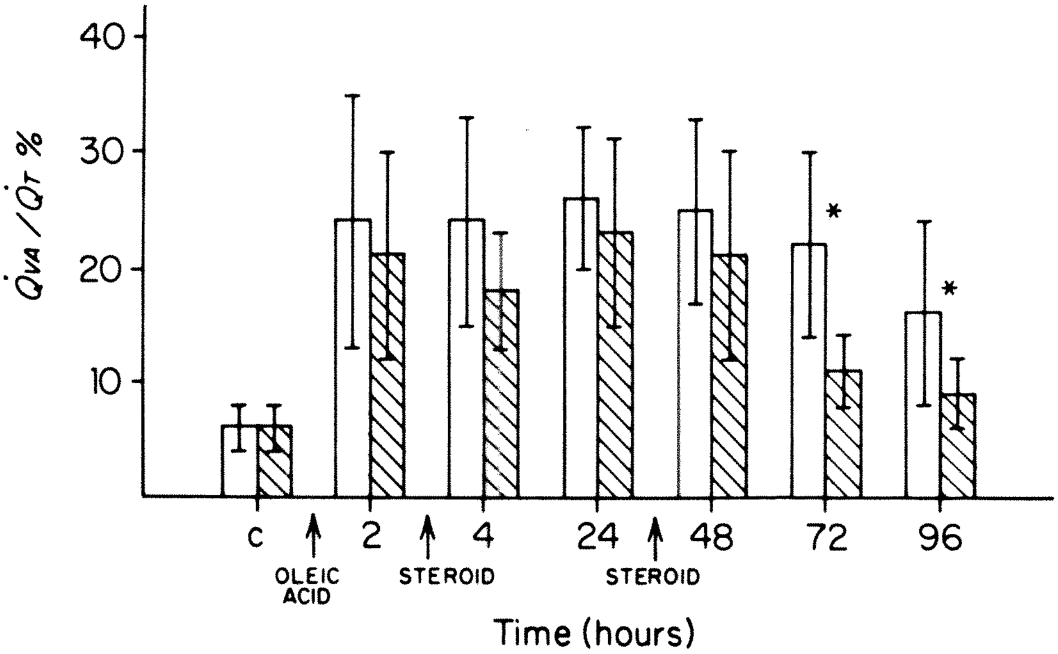


FIG. 1. Mean values for venous admixture ($\dot{Q}_{VA}/\dot{Q}t$) ± standard deviation before and after intravenous oleic acid. Solid bars: untreated. Stripped bars: steroids. *$p < 0.001$ between values for untreated and steroid treated at 72 hours and $p < .05$ at 96 hours.

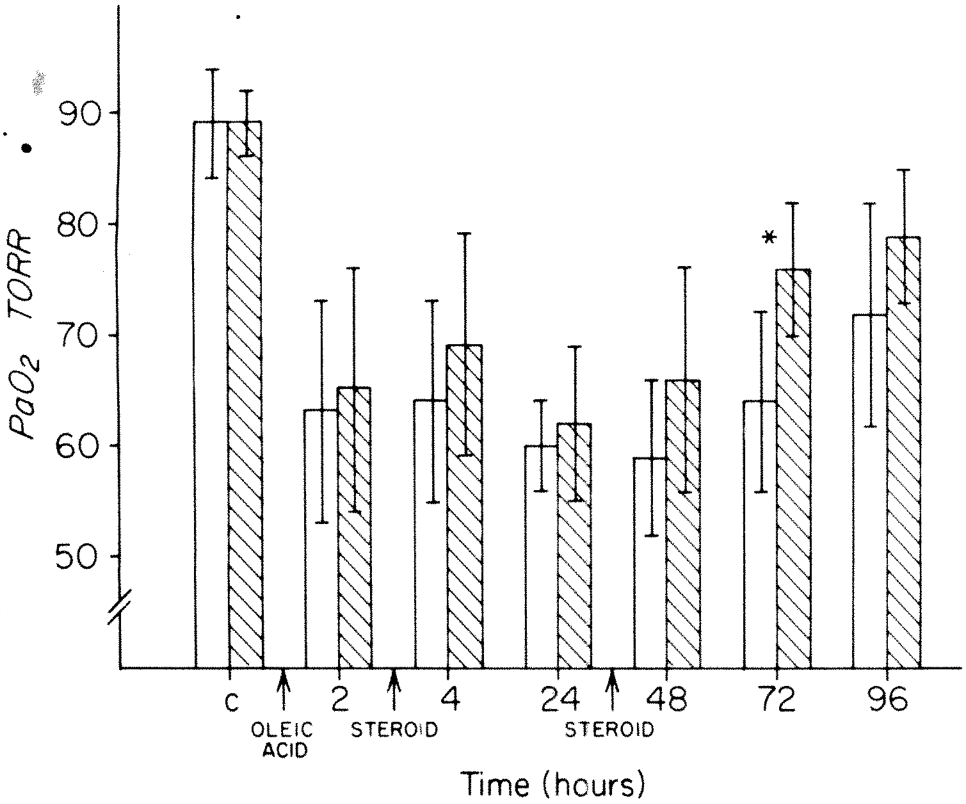


FIG. 2. Mean Pa_{O_2} values ± standard deviation before and after intravenous oleic acid. Solid bars: untreated. Stripped bars: steroids. $^*p < 0.001$ between values for untreated and steroid treated.

creased in both groups of animals immediately after administration of oleic acid (Fig. 5) but 24 hours after oleic acid injection, $\dot{Q}t$ had returned to control levels in both treated and untreated animals. The only significant difference in cardiac output between treated and untreated animals was at 48 hours when the steroid treated animals had a small but significantly higher $\dot{Q}t$. In the untreated animals, mean pulmonary artery pressure ($\overline{PAP}$) increased over preoleic acid values at two and four hours, then decreased so there was no

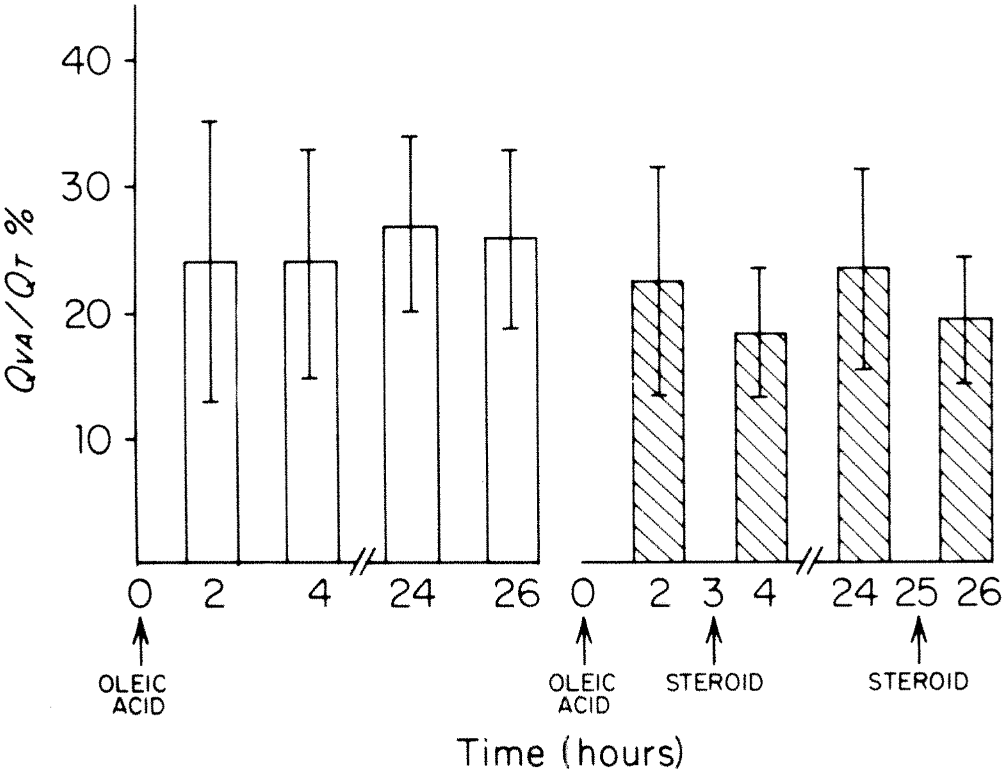


FIG. 3. Mean values for venous admixture ($\dot{Q}_{VA}/\dot{Q}t$) ± standard deviation before and after administration of methylprednisolone in the treated animals. Values for the untreated animals over the same time period are shown for comparison. Solid bars: untreated. Stripped bars: steroids.

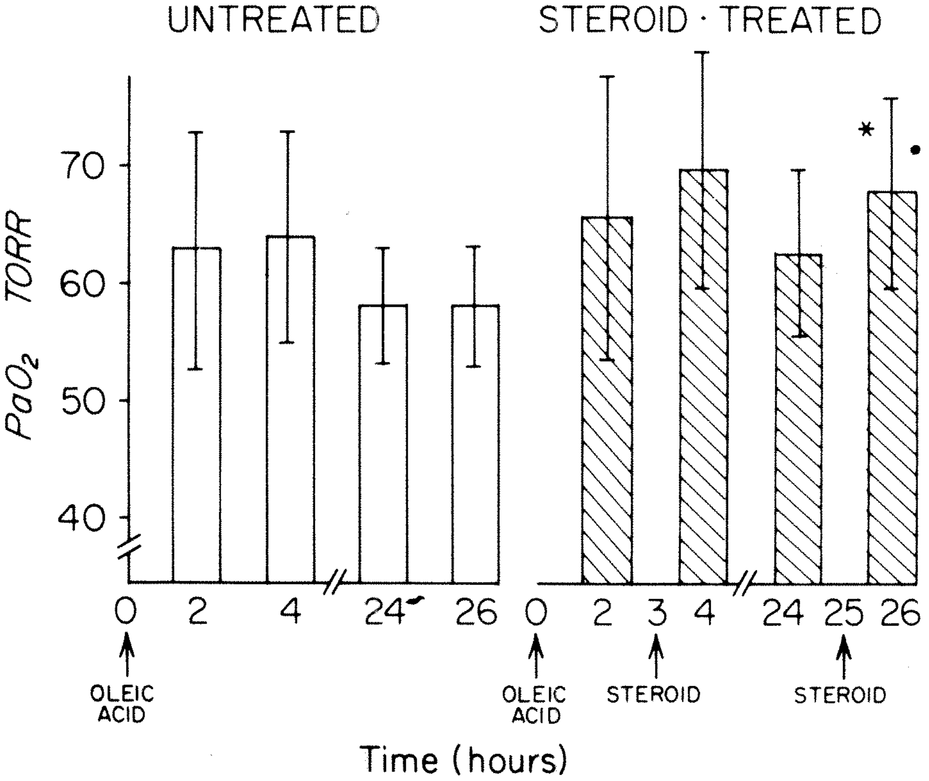


FIG. 4. Mean values for Pa_{O_2} ± standard deviation before and after administration of methylprednisolone. Values for the untreated animals over the same time are shown for comparison. Solid bars: untreated. Stripped bars: steroids. $*p < 0.05$ between values.

significant difference from control at 24 hours and for subsequent measurements (Table 1). Mean pulmonary artery pressure of untreated animals was slightly higher at 96 hours than the $\overline{PAP}$ of treated animals. There were essentially no differences in mean blood pressure, heart rate, Pa_{CO_2}, and pH between the two groups (Table 1).

Gross postmortem examination of the lungs in both groups showed congestion with focal areas of hemorrhage and necrosis. Edema fluid exuded from the cut surface of the lung. Both treated and untreated animals had significantly higher lung water/dry weight ratios than control values for normal dog (Table 2). There was no difference however, in lung water/dry weight ratios

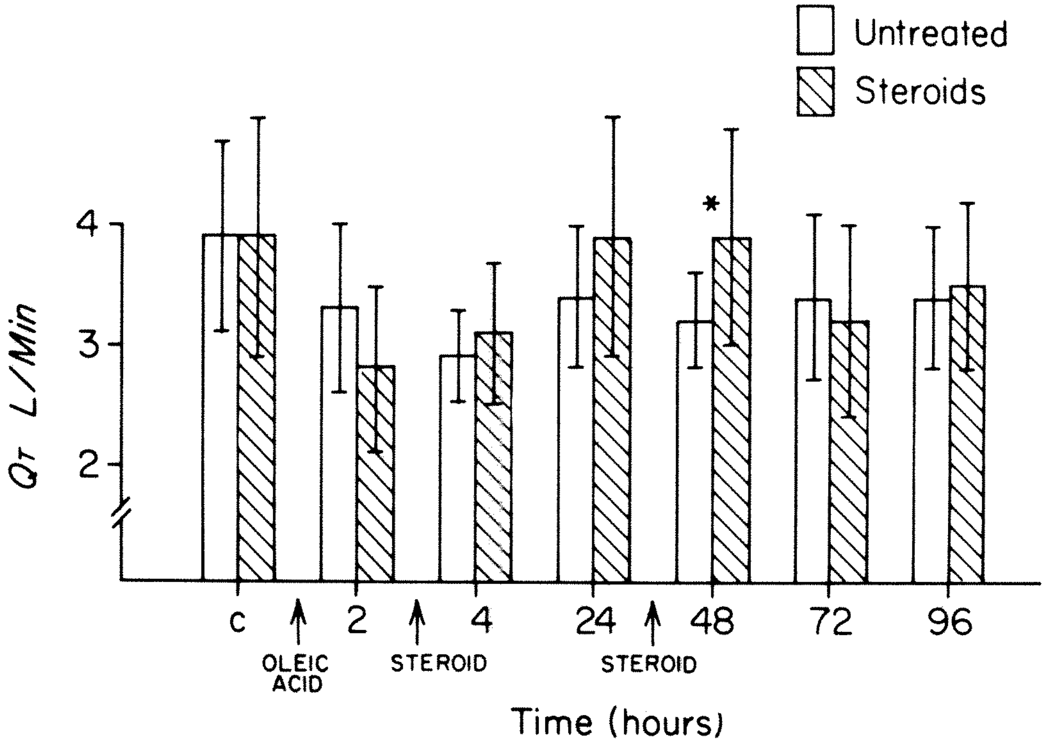


FIG. 5. Mean values for cardiac output ($\dot{Q}t$) ± standard deviation before and after intravenous oleic acid. Solid bars: untreated. Stripped bars: steroids. $*p < 0.05$ between values for untreated and steroid treated.

TABLE 1. *Mean Values for Mean Pulmonary Artery Pressure ($\overline{PAP}$), Pa_{CO_2}, Arterial pH, Mixed Venous Oxygen Tension ($P\bar{v}_{O_2}$), Heart Rate (HR), and Mean Arterial Blood Pressure ($\overline{BP}$) Prior to and After 0.06 ml/kg Oleic Acid*

		Control	2 Hours	4 Hours	24 Hours	48 Hours	72 Hours	96 Hours
$\overline{PAP}$	Untreated	17 ± 4	23 ± 5*	28 ± 14*	25 ± 19	19 ± 4	17 ± 4	20 ± 6
cm H_2O	Treated	14 ± 4	23 ± 8	24 ± 12	18 ± 6	20 ± 7	15 ± 4	14 ± 4†
Pa_{CO_2}	Untreated	35 ± 2	37 ± 5	35 ± 5	35 ± 3	34 ± 4	34 ± 4	34 ± 4
(Torr)	Treated	36 ± 4	35 ± 6	30 ± 6*	34 ± 4	36 ± 3	34 ± 6	35 ± 5
pHa	Untreated	7.38 ± .03	7.38 ± .04	7.39 ± .04	7.39 ± .03	7.39 ± .03	7.39 ± .02	7.38 ± .02
	Treated	7.39 ± .04	7.37 ± .05	7.42 ± .04*	7.42 ± .06	7.39 ± .04	7.40 ± .03	7.41 ± .03
$P\bar{v}_{O_2}$	Untreated	39 ± 5	34 ± 4	35 ± 6	33 ± 3	32 ± 4	33 ± 4	36 ± 4
(Torr)	Treated	37 ± 3	33 ± 6	34 ± 5	33 ± 5	35 ± 5	34 ± 4	34 ± 5
HR	Untreated	99 ± 24	102 ± 31	118 ± 36	122 ± 44	102 ± 36	97 ± 38	93 ± 34
	Treated	104 ± 27	139 ± 26†	140 ± 16*	104 ± 23	83 ± 20	96 ± 40	118 ± 36
$\overline{BP}$	Untreated	110 ± 20	113 ± 16	113 ± 14	102 ± 12	102 ± 36	97 ± 38	93 ± 34
(Torr)	Treated	114 ± 13	117 ± 13	115 ± 9	98 ± 10*	83 ± 20†	96 ± 40	118 ± 36

Treated group received 30 mgm/kg methylprednisolone 3 and 25 hours after oleic acid injection. N = 11 in both groups.

* $p < .05$ compared with preoleic acid control measurements.
† $p < .05$ between steroid treated and untreated.

between treated and untreated (Table 2). Microscopic examination of the lung sections in both groups revealed extensive but patchy alveolar edema and hemorrhage. The alveolar space was filled with red blood cells and eosinophilic proteinaceous material. Where alveolar septae were necrotic, no nuclear profiles were discernable. Occasional polymorphonuclear leukocytes were noted within the alveolar septae, but there were none within the alveolar space. There was a variable degree of cellular proliferation, predominately epithelial cells at the periphery of necrotic and hemorrhagic areas. These cells were cuboidal to low cuboidal in shape, with abundant basophilic cytoplasm, presumably representing Type II (granular) pneumocytes. The degree of cellular proliferation was scored from 0 to 4+ as described in the Methods section. The most striking difference between treated and untreated animals was in the increased amount of cell proliferation in the treated animals. The mean cell proliferation score for the treated was 3.43 ± 1.13 (SD) and for the untreated 2.0 ± 1.0. The difference was significant ($p < .05$) when compared with the Student's unpaired t-test. A representative histologic section of the lung of an untreated animal (Fig. 6) is compared with that of a treated animal in Figure 7 and shows the marked increase in Type II cell proliferation in the treated.

Discussion

Animals treated with methylprednisolone in this study had markedly improved gas exchange 72 hours after lung injury compared to untreated animals. In spite of the fact $\dot{Q}_{VA}/\dot{Q}t$ was significantly lower in steroid treated animals at 96 hours, direct lung water measurements made at that time showed no difference between treated and untreated. This suggests that *in vitro* gravimetric measurements of lung water may not accurately reflect the gas exchanging capability of the lung *in vivo*. Other studies[3,8] have shown that corticosteroids decrease mortality from oleic acid injury in dogs but the delayed improvement in gas exchange until 72 hours and microscopic evidence of resolution of the injury at 96 hours have not been previously described.

In a study similar to ours, Jones and King[8] administered methylprednisolone to pentobarbital anesthetized dogs 75 and 165 minutes after an injection of 0.075 ml/kg oleic acid into the right ventricle.[8] Ten of 11 steroid treated animals survived the four day study period, while only three of the nine untreated animals survived. Although the number of survivors was small, when the animals were studied at 96 hours $\dot{Q}_{VA}/\dot{Q}t$ with the animals breathing room air was significantly lower in the treated group. The mortality in both treated and untreated animals in Jones and King's study may have been related to the six hours of general anesthesia to which the animals were subjected during and immediately after lung injury. This finding suggests that pentobarbital anesthesia itself and/or six hours of immobilization might have a deleterious effect, as we observed no mortality in either treated or untreated animals with about the same degree of lung injury.

Bradley[3] induced a more severe lung injury than that in our study by injecting 0.15 ml/kg oleic acid into unanesthetized dogs. Animals who received intravenous dexamethasone immediately after oleic acid had a 30% mortality while untreated animals had a 64% mortality. Pa_{O_2} values were significantly lower in the untreated animals from 1–48 hours after injury. The immediate improvement in Pa_{O_2} in Bradley's study may have been related to the immediate therapy with steroids,

TABLE 2. *Values ± SD for Lung H_2O/Dry Weight Ratio for Normal Dog Lung, Untreated and Steroid Treated Dogs 96 Hours after Oleic Acid Injection*

Normal Dog Lung	3.94 ± 0.46	n = 10
Untreated	5.29 ± 0.31*	n = 10
Steroid Treated	5.29 ± 0.40*	n = 11

* $p < .05$ compared with normal dog lung. n = number of animals.

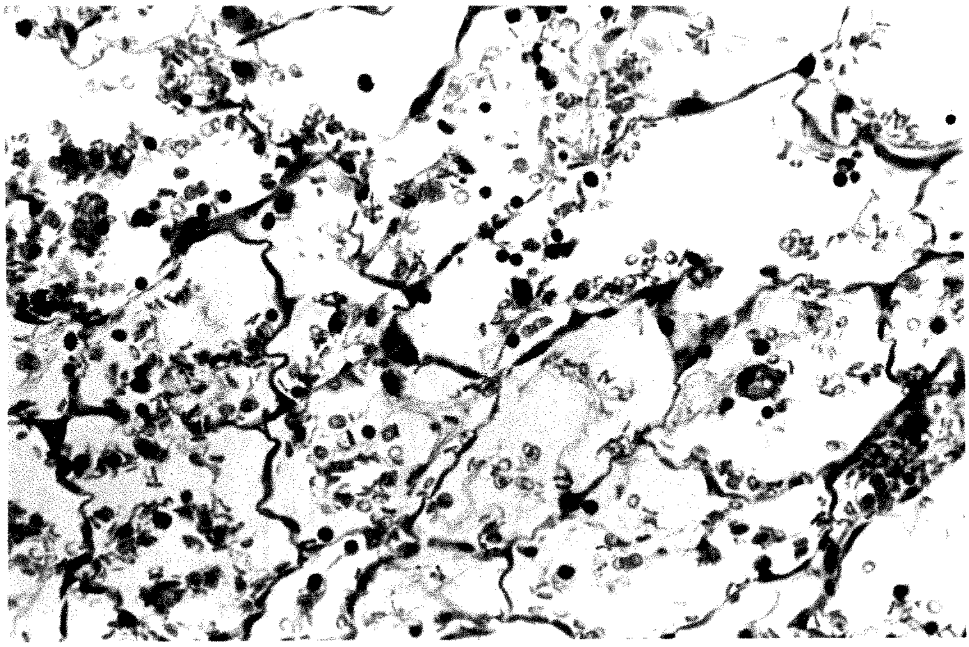


FIG. 6. Microscopic section of a representative lung of an untreated animal 96 hours after injury. Alveoli are filled with proteinaceous edema fluid and occasional red blood cells. Rare Type II pneumocytes are seen. Magnification ×360.

whereas the animals in our study were not treated until three hours after injury.

Although we found no difference in the amount of lung water between treated and untreated animals 96 hours after oleic acid injury, other studies[12,19] have shown an immediate effect of corticosteroids on the amount of pulmonary edema observed after oleic acid injection. Wertzberger and Peltier[19] observed that the pulmonary edema and hemorrhage in rats 24 hours after oleic acid injection was significantly less in animals pretreated with intramuscular cortisone and hydrocortisone. Kreis et al.[12] administered 3 mg/kg intravenous methylprednisolone to pentobarbital anesthetized dogs simultaneously with oleic acid. These investigators observed that the Pa_{O_2} in steroid treated animals one to four hours after lung injury was significantly higher than animals who had oleic acid only. Microscopic examination of the lungs four hours after injury showed markedly less congestion and hemorrhage in steroid treated animals as compared to untreated controls. The immediate effects of steroids in reducing pulmonary edema and improving Pa_{O_2} in these studies[12,19] may be related to the fact that the steroids were administered prior to, or almost simul-

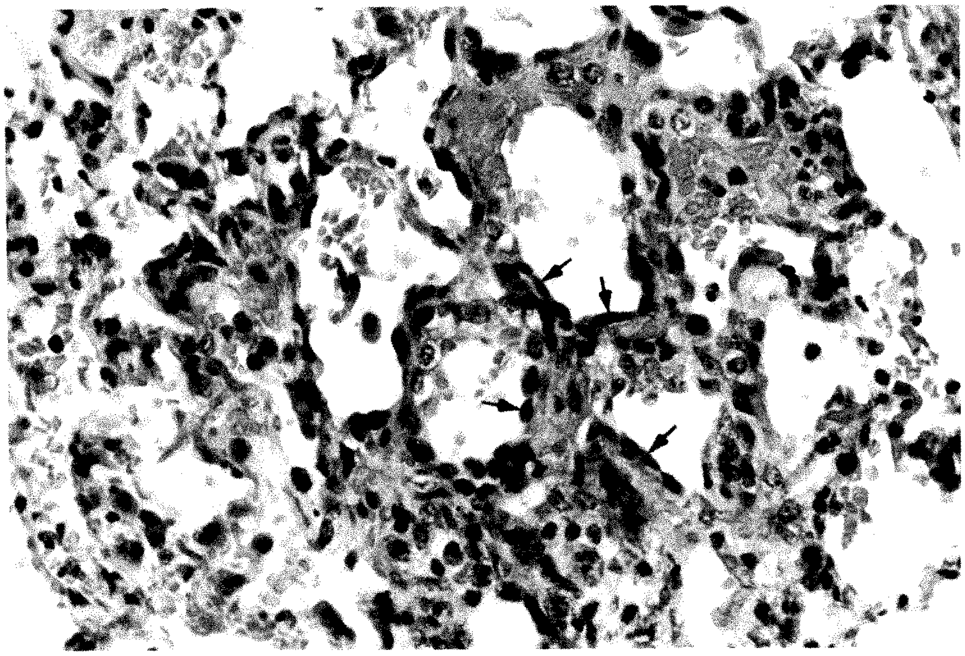


FIG. 7. Microscopic section of a representative lung of a methylprednisolone treated animal 96 hours after injury. Alveoli are relatively free of proteinaceous edema fluid. Cuboidal cells (arrowheads) with abundant basophilic cytoplasm, presumably Type II pneumocytes, form a continuous lining of the alveolar space. Magnification ×360.

taneously with, the oleic acid. In our study methylprednisolone was not administered until 3 hours after lung injury. We chose the 3 hour time interval in order to allow the lesion to become established prior to administering steroids as we believed this a more clinical relevant circumstance.

The beneficial effects[3,12,19] of early treatment with steroids on survival, Pa_{O_2}, and pulmonary edema in oleic acid lung injury may represent one pharmacologic action of corticosteroids while our study, showing only a late effect, may represent another action. In the case of pretreatment corticosteroids may exert their effect by stabilizing the lysosomal membranes of polymorphonuclear leukocytes, thus decreasing the amount of pulmonary injury due to release of proteolytic enzymes from the leukocytes.[20] However, once the lesion is established for three hours prior to corticosteroid administration, stabilization of lysosomal membranes may have no effect on the injury. The sequence of morphologic events observed in oleic acid induced alveolar injury[5,17] is almost identical with those of other alveolar injury.[7] Necrosis of Type I pneumocytes is followed by proliferation of Type II pneumocytes, which repopulate the basal lamina scaffold. Proliferation of Type II pneumocytes is the initial step in the repair of alveolar injury. The mechanism of the late improvement in pulmonary injury observed in our study is probably due to methylprednisolone induced proliferation and maturation of granular Type II pneumocytes, which we observed in the treated animals 96 hours after injury. There are substantial experimental data[9,11,18] and some clinical experience[6,13] indicating steroids promote Type II pneumocyte proliferation and maturation in the fetus and are beneficial in prevention and treatment of the infant respiratory distress syndrome. Initially, it was thought that the effects of corticosteroids on the lungs may be limited to the fetal period since the density of steroid receptors in the lungs seems to drop precipitously during the neonatal period. Recently it has been shown that adult lungs of a number of animal species contain a high density of steroid receptor sites.[2] These data strongly suggest corticosteroids may also stimulate Type II pneumocyte proliferation in adult lung following alveolar injury. The proliferating Type II pneumocytes may provide a new permeability barrier, preventing further leakage of alveolar edema fluid and the surfactant secreted by Type II pneumocytes may further stabilize alveolar geometry and improve aeration of alveoli. These effects may lead to the improved physiologic data observed in our study.

There is clinical evidence to suggest that corticosteroids have a beneficial effect on pulmonary function when administered prophylactically in the fat embolism syndrome.[16] The present study suggests that even after lung injury has become established, corticosteroids will speed resolution of the injury even though there is no immediate benefit on pulmonary function. Our animal data indicates that even after hypoxemia has occurred from the pulmonary injury, methylprednisolone will hasten resolution of the hypoxemia significantly earlier than in untreated animals.

References

1. Ashbaugh, D. G. and Uzawa, T.: Respiratory and Hemodynamic Changes After Injection of Free Fatty Acids. J. Surg. Res., 8:417, 1968.
2. Ballard, P. L.: Glucocorticoid Receptors in the Lung. Fed. Proc., 36:2660, 1977.
3. Bradley, B. E., Jr., Vracko, R., Sullivan, K. N. et al.: Corticosteroids as Treatment for Chemical Pneumonitis Induced by Intravenous Oleic Acid. Clin. Orthop., 86:230, 1972.
4. Comroe, J. H.: Physiology of Respiration (second ed.). Chicago, Year Book Medical Publishers, 1974. pp. 316.
5. Derks, C. M., Jacobovitz-Derks, D.: Embolic Pneumopathy Induced by Oleic Acid: A Systematic Morphologic Study. Am. J. Pathol., 87:143, 1977.
6. Howie, R. N., Liggins, G. L.: Prevention of respiratory distress syndrome in premature infants by antepartum glucocorticoid treatment. *In* Villee, C. A., Villee, D. B., Zuckerman, J., (eds.) Respiratory Distress Syndrome, New York, Academic Press, 1973. pp. 369–380.
7. Huang, T. W., Carlson, J. R., Bray, T. M. et al.: 3-Methylindole-induced Pulmonary Injury in Goats. Am. J. Pathol., 87:647, 1977.
8. Jones, R. L. and King, E. G.: The Effects of Methylprednisolone on Oxygenation in Experimental Hypoxemic Respiratory Failure. J. Trauma, 15:297, 1975.
9. Kikkawa, Y., Kaibara, M., Motoyama, E. K. et al.: Morphologic Development of Fetal Rabbit Lung and its Acceleration with Cortisol. Am. J. Pathol., 64:423, 1971.
10. King, E. G., Wagner, W. W., Ashbaugh, D. G. et al.: Alterations in Pulmonary Microanatomy After Fat Embolism. Chest, 59:524, 1971.
11. Kotas, R. V. and Avery, M. E.: Accelerated Appearance of Pulmonary Surfactant in Fetal Rabbit. J. Appl. Physiol., 30:358, 1971.
12. Kreis, W. R., Lindenauer, S. M. and Dent, T. L.: Corticosteroids in Experimental Fat Embolization. J. Surg. Res., 14:238, 1973.
13. Liggins, G. C. and Howie, R. N.: A Controlled Trial of Antepartum Glucocorticoid Treatment for Prevention of Respiratory Distress Syndrome in Premature Infants. Pediatrics, 50:515, 1972.
14. Ruiz, B. C., Tucker, W. K. and Kirby, R. R.: A Program for Calculation of Intrapulmonary Shunts, Blood-gas, and Acid-base Values with a Programmable Calculator. Anesthesiology, 42(1):88, 1975.
15. Shapiro, H. M., Smith, G., Pribble, A. H. et al.: Errors in Sampling Pulmonary Arterial Blood with a Swan-Ganz Catheter. Anesthesiology, 40:291, 1974.
16. Shier, M. R., Wilson, R. F., James, R. E. et al.: Fat Embolims Prophylaxis: A Study of 4 Treatment Modalities. J. Trauma, 17:621, 1977.
17. Vracko, R.: Significance of Basal Lamina for Regeneration of Injured Lung. Virchows Arch. Pathol. Anat. 355:264, 1972.
18. Wang, N. S., Kotas, R. V., Avery, M. E. et al.: Accelerated Appearance of Osmiophilic Bodies in Fetal Lungs Following Steroid Injection. J. Appl. Physiol., 30:362, 1971.
19. Wertzberger, J. J. and Peltier, L. F.: Fat Embolism: The Effect of Corticosteroids on Experimental Fat Embolism in the Rat. Surgery, 64:143, 1968.
20. Wilson, J. W.: Treatment of Prevention of Pulmonary Cellular Damage with Pharmacologic Doses of Corticosteroids. Surg. Gynecol. Obstet., 134:675, 1972.

Revascularization of the Ischemic Canine Hindlimb by Arteriovenous Reversal

KAJ JOHANSEN, M.D., PH.D., EUGENE F. BERNSTEIN, M.D., PH.D.

Arteriovenous reversal (AVR) for revascularization of ischemic tissues has previously failed to meet theoretical, experimental, and clinical expectations despite recurrent trials. The efficacy of a new staged approach to AVR was tested against a canine ischemic limb preparation in which global ligation of ipsilateral collaterals inevitably led to limb gangrene. In 12 animals the complications of direct, single-stage end-to-end femoral AVR, inevitably accompanied by the development of extreme edema, were demonstrated. However, when the ischemic preparation was accompanied by a staged AVR, in which an initial end-artery-to-side-vein arteriovenous fistula was converted 1 week later to AVR by ligation of the central venous limb, 20 of 20 animals survived, and 19 of 20 were ambulatory long-term survivors with only mild edema. Serial angiograms at 1 week, 1 month, and 4 months demonstrated patency rates of 100, 84, and 63%, respectively. Histologic examination of animals electively killed from 4 to 24 months showed normal skeletal muscle histology, venous intimal thickening, and mild edema. In the acutely ischemic canine hind limb, a staged AVR can provide both viability and function with only mild edema formation.

From the Department of Surgery, University of California, San Diego, School of Medicine, La Jolla, California.

STANDARD TECHNIQUES for arterial reconstruction are generally of no avail when arterial occlusive disease is extensive and diffuse in its involvement of large and small arteries alike. In the extremities, such circumstances usually advance to tissue ischemia and gangrene. Despite multiple imaginative attempts at direct or collateral tissue revascularization, amputation usually has been the final therapeutic maneuver. For more than eight decades, attempts have been made to utilize an alternate, nondiseased pathway to the capillary bed—the venous tree. Arteriovenous reversal (AVR) of blood flow in the canine hindlimb was tested as a potential revascularization technique in the current study.

Methods

Several different studies were designed to discern whether AVR can perfuse tissues previously rendered ischemic. This required the initial development of a *control* canine hind limb preparation in which irreversible tissue ischemia and gangrene were unavoidable without further intervention. Only by so doing could the effects seen with further manipulations properly be ascribed to the manipulation itself and not to the presence of collateral vessels. Clinical, physiologic, and pathologic criteria regarding tissue nutrition, flow distribution, and the effects of such reversed flow on both vessels and tissues were monitored serially.

Fifty-six conditioned mongrel dogs were used for these experiments. Throughout, the precepts promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources of the National Academy of Sciences/National Research Council, as outlined in the *Guide for Laboratory Animal Facilities and Care*, were followed, and the animals' condition was monitored daily by licensed veterinarians of the Office of Animal Resources, UCSD School of Medicine.

Group I. Control Ischemic Limb Preparation

Twelve male and female mongrel dogs weighing 15–25 kg were used to develop a reliable model for an ischemic limb that would undergo irreversible tissue death in the absence of a further therapeutic intervention. After an overnight fast, the animals were sedated with 2 cc intramuscular Innovar* and 0.5 mg atropine and then were anesthetized with 25 mg/kg intravenous pentobarbital,† further intravenous pentobarbital being administered incrementally during the course of the surgical procedure as needed. Heparin was administered (100 u/kg).

Reprint requests to Kaj Johansen, M.D., Ph.D., Department of Surgery, University of Washington, Harborview Medical Center, Seattle, Washington.

Submitted for publication: September 22, 1978.

* Pitman-Moore, Washington Crossing, New Jersey.

† Diamond, Great Neck, New York.

0003-4932/79/0800/0243 $01.05 © J. B. Lippincott Company

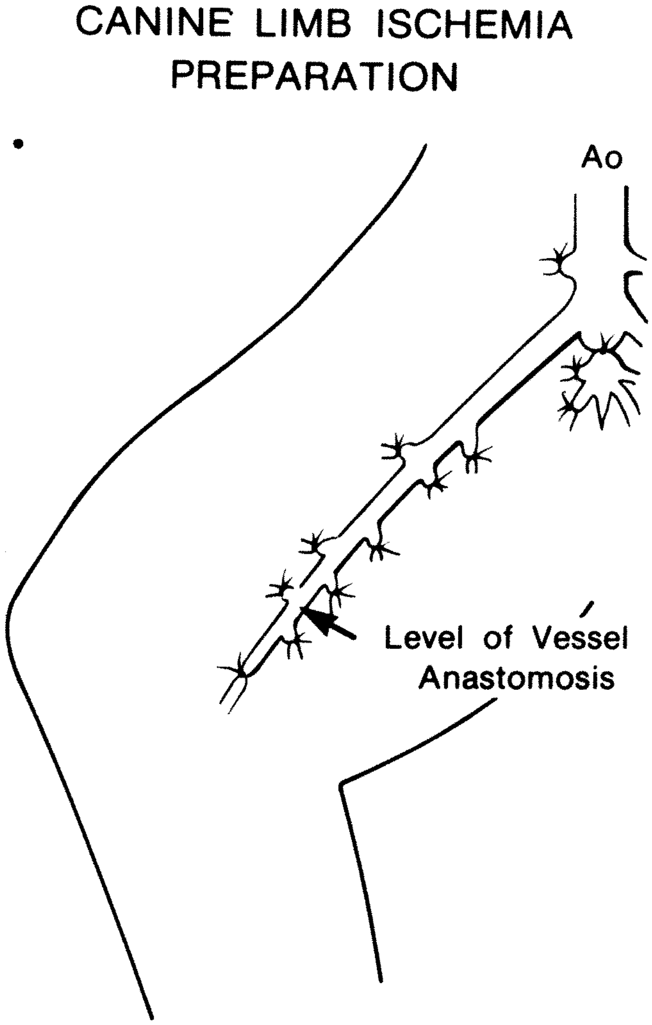


FIG. 1. Scheme of collateral and peripheral femoral artery ligation that resulted in irreversible ischemia in the Group I animals.

In all animals the femoral artery was ligated and divided as far peripherally as possible in the adductor canal of one leg. More central arterial branches were also ligated and divided. Although initial attempts at limb devascularization were limited to denuding just the common femoral artery of its branches (up to the level of the inguinal ligament), inability to render the limb ischemic led to higher and higher ligations of branch arteries. Ultimately an irreversibly ischemic limb preparation was developed and applied in seven dogs (Group I) in which the following criteria were met: 1) The limb was functionless: the animal neither bore weight nor walked on the operated legs; and 2) the limb progressed to irreversible gangrene, or the animal died. To achieve these criteria, the final preparation (Fig. 1) involved ligature of the peripheral femoral artery and all femoral artery branches in the thigh, as well as ligature of the terminal aorta, both internal iliac arteries, the last ipsilateral lumbar artery, and the ipsilateral deep circumflex iliac artery. The dogs were examined twice daily for evidence for limb viability, weight-bearing, and general clinical condition. A complete necropsy was performed on all animals, and specimens of skin and skeletal muscle were processed for microscopic examination.

Group II. Immediate Arteriovenous Reversal

Twelve mongrel dogs of both sexes, weighing 15–25 kg, underwent procedures combining limb devascularization as described for Group I with a surgical maneuver designed to provide immediate retrograde flow of arterial blood to the venous circulation of the limb.

All animals were sedated and anesthetized as described previously. Heparin was administered (100 u/kg) and the femoral artery and the femoral vein were isolated in the adductor canal of the left leg. These vessels were divided, and the central arterial end and the peripheral venous end were anastomosed. In these animals, complete ipsilateral devascularization, as described in Group I animals, was performed as well.

After the operations, daily examinations of limb viability were carried out. Doppler ultrasonography‡ was utilized in several animals to investigate the peripheral progression of the arterial pulse velocity. Weight-bearing and exercise tolerance, skin temperature, wound healing, and palpable arterial pulsation were recorded daily for each animal, and limb circumference 10 cm above and 5 cm below the tibial tubercle was measured and recorded. The presence of subcutaneous hemorrhage and skin necrosis was gauged clinically and graded from 0 to 4+. Angiography was performed in one animal. Either electively or because of impending gangrene, all these animals were killed with 1 mg/kg of intravenous pentobarbital at periods of time up to six weeks after the operation, and necropsy examinations were performed.

Group III. Staged Arteriovenous Reversal

Because one-stage AVR (Group II) had an unacceptably high mortality and morbidity, 32 animals were used to develop a technique of staged AVR adapted from a description by Hiertonn.[8] Twenty animals comprise Group III. In the first stage the femoral artery was divided in the adductor canal and the peripheral end was ligated. An elliptical 6 mm defect was created in the lateral wall of the common femoral vein, and the artery was anastomosed end-to-side to the vein. A 2-0 silk ligature, ends left long, was loosely passed twice around the central venous limb of this end-to-side arteriovenous fistula (AVF) just above the area of anastomosis. Limb devascularization was performed as previously described, and the wound was closed with the long ends of the 2-0 silk suture left outside the fascia, beneath the skin closure. On postoperative day six or seven the wound was reopened under Innovar sedation (2 cc intramuscularly), the long ends of the 2-0 silk suture were located, and the central venous limb of the AVF was ligated, producing true AVR (Fig. 2).

---

‡ Medsonics, Mountain View, California.

In eight Group III animals, electromagnetic flowmeter probes§ were used to measure flows in the femoral artery before and after AVF formation during the first stage, and immediately and seven days following ligation of the central venous limb of the AVF. Serial direct femoral puncture angiography was performed in all animals one to two and six to ten weeks after the second stage procedure. In addition, at 10–12 weeks after operation, seven animals underwent transcarotid catheter arteriography using a high-speed film changer (Westinghouse) and an automatic injector system.¶ Patency of each of the AVRs was investigated, and collateral vessel formation was graded on sequential films from 0 to 4+ and tabulated.

As before, the animals were examined daily for the first two weeks after the operation and then weekly thereafter, with tabulation of exercise tolerance, wound healing, skin temperature, and the presence of peripheral pulses as indicated by digital palpation and by Doppler ultrasonography. Limb circumference was carefully tabulated at points 10 cm above and 5 cm below the stifle ("knee"). The animals were serially killed at periods up to 24 months after operation. From selected animals, specimens of skin, muscle, and appropriate blood vessels were taken for pathologic examination.

Results

Group I. Control Ischemic Limb Preparation

In Group I animals, in which a reproducible limb gangrene preparation was attempted, initial attempts demonstrated the remarkable proclivity of the dog to re-establish blood flow to an ischemic area by means of collaterals. However, in the last seven dogs in which complete devascularization was performed, the limbs were cold, tender, and functionless, and the animals never stood or bore weight. Angiography performed on one animal showed a thrombosed femoral artery and no sign of significant collateral ingrowth. All seven animals died or were killed in one to six days because of their clearly terminal state. Specimens of skin and muscle demonstrated early mild to moderate necrosis.

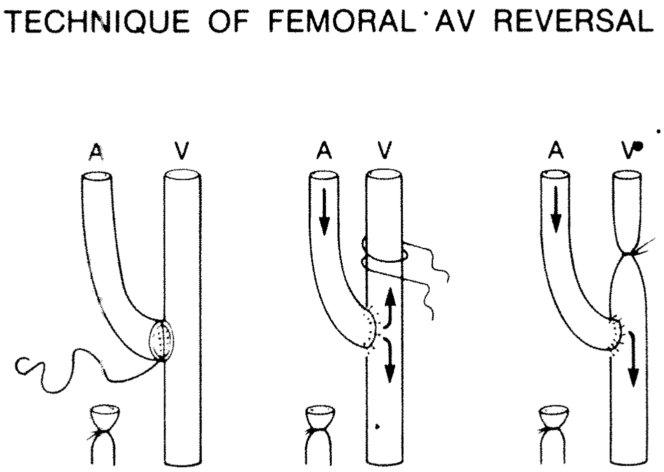


FIG. 2. Staged arteriovenous reversal, the Group III preparation, was accomplished by end-artery-to-side-vein fistula (*left*) and placement of loose suture around the proximal vein (*center*) in an initial sitting. A week later, the venous ligature was tightened (*right*) to complete the procedure.

Group II. Immediate Arteriovenous Reversal

Group II animals underwent procedures designed to explore the utility of immediate AVR for limb salvage. These animals consistently developed almost immediate massive edema with average lower leg circumference rising from a control value of 18.67 ± 0.5 cm to 28.71 ± 1 cm on the third postoperative day (153.7% greater than control), peaking on day 9 at 32.35 ± 1.5 cm (172.7% of control). The progression of edema formation with time in both the upper and lower leg is shown in Figure 3. In all cases the animal's limbs were cool and so swollen that usual anatomic land-

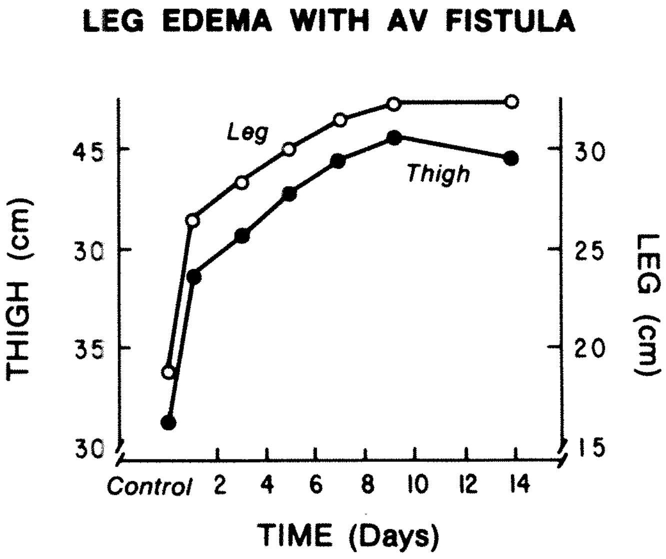


FIG. 3. Massive unrelenting limb edema followed simple AV fistula (Group II) operation.

---

§ Statham, Hato Rey, Puerto Rico.

¶ Medrad, Allison Park, Pennsylvania.

TABLE 1. *Cumulative Data from Group II Dogs, Immediate AVR*

Dog No.	Circumferences C/c* Day 0	Day 1	Day 3	Day 7	Day 14	Stand/Weight Bearing (Day)	Skin Necrosis	Skin Hemorrhage	Time of Death (killing)
II-1	30/18	36/24	38/26	40/28	†	Never	+++	++	8 days
II-2	34/20	39/26	43/28	46/30	†	2 days	+++	++	9 days
II-3	31/20	38/30	†	—	—	Never	0	+++	(3 days)‡
II-4	34/20	39/26	40/28	46/31	46/31	3 days, living	0	+	(5 wk)
II-5	30/17	36/22	37/26	42/32	40/30	2 days, living	0	++	(6 wk)§
II-6	28/15	—	—	†	—	0	++	++++	7 days
II-7	32/20	40/28	43/32	48/35	47/36	8 days, living	0	++	(5 wk)
II-8	30/18	†	—	—	—	0	0	+	1 day‡
II-9	34/20	40/28	42/30	46/33	45/32	6 days, living	0	++	(3 wk)
II-10	30/17	†	—	—	—	0	0	++	1 day
II-11	30/19	42/29	†	—	—	0	++	+++	3 days‡
II-12	32/20	40/29	42/31	†	—	0	+++	++++	(5 days)
n	12	9	7	6	4				
Mean C	31.25	38.89	40.71	44.67	44.50				
Mean c	18.67	26.89	28.71	31.50	32.35				
SEM	0.59	0.69	0.99	1.34	1.38				
SEM	0.50	0.92	0.96	1.08	1.52				

* C, 10 cm above tibial tubercle; c, 5 cm below tibial tubercle.
† Animal found dead, or killed.
‡ Arteriovenous reversals patent at necropsy.
§ Animal found to have thrombosed AVR, profuse collateral vessel formation on immediate postmortem arteriogram.

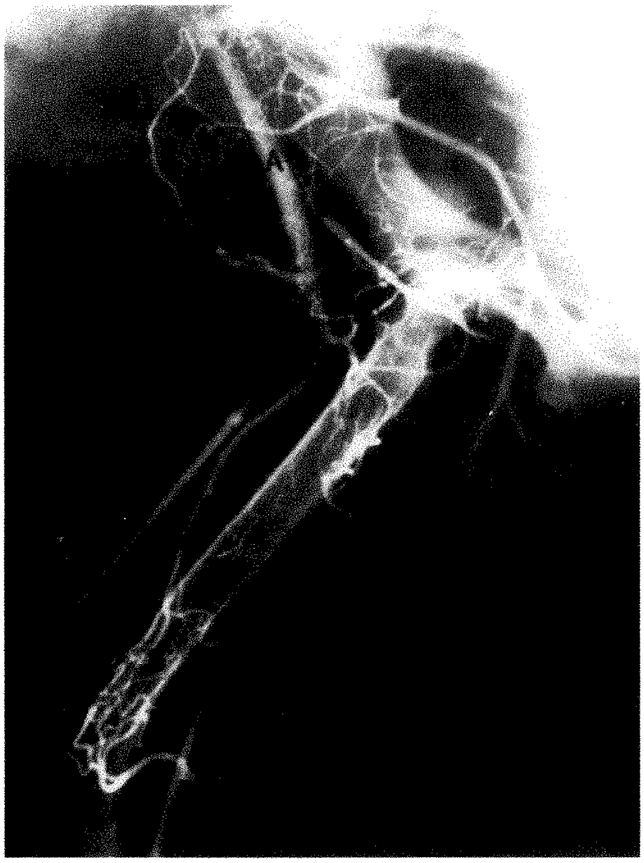


FIG. 4. Angiography in a Group II dog. Femoral artery (FA) injection (*A*) shows obliteration of main channel of venous tree, but rich collateral formation peripherally (*B*) with FA reconstitution.

marks were effaced, wound healing was poor, and the limbs were minimally functional, even in the long-term survivors. The animals frequently manifested significant subcutaneous hemorrhage and skin necrosis, as noted in Table 1. Doppler ultrasonography failed to reveal a pulse peripheral to the site of anastomosis after the third postoperative day in any animal. The animals generally declined to bear weight on the operated leg, and apparent sepsis appeared to supervene in several cases. Eight of the 12 animals died or were put to death within two weeks. Necropsy showed massive edema and nonviable muscle, and muscle necrosis was demonstrable by microscopy. Four animals survived: edema subsided slightly, but neither limb circumference nor function returned to normal, though these animals bore weight with a limp. Angiography performed on one of these animals showed profuse collateral development and thrombosis of the AV communication (Fig. 4). Of the 12 animals, only 3 had patent AV anastomoses at the time of necropsy.

Group III. Staged Arteriovenous Reversal

Group III animals underwent procedures designed to explore the use of a staged AVR preparation for limb salvage; formation of an initial arteriovenous fistula (AVF) was followed in 1 week by ligation of the central venous limb of the AVF, thereby creating a "delayed" AVR. Limb devascularization was performed at the first sitting. All 20 animals survived operation and 19 were long-term survivors. One animal was found dead in his cage 1 week after the second operation; he had previously seemed healthy and had walked without difficulty on his operated leg. Necropsy failed to reveal a cause for death. The AV anastomosis was intact and patent, and skin and skeletal muscle seemed viable. Minimal edema was present, with the limb circumference of the operated leg 4% greater than control. Microscopic examination of tissue was not done.

All Group III animals stood shortly after AVF formation, but only 6/20 bore weight normally; all manifested evidence for ongoing discomfort in the limb, attempting to avoid manipulation or examination. Wound healing was excellent and occurred *per primam*. After conversion to AVR, all animals stood within 12 hours and 16/20 bore weight on the reoperated limb within that period: within 1 week all animals walked without obvious limb dysfunction. This general clinical impression of normal function was maintained indefinitely thereafter.

All animals manifested mild edema after AVF formation, with initial lower limb circumference of 18.65 ± 0.2 cm rising to 20.05 ± 0.4 on day 3 (107.5% of control), 21.75 ± 0.5 cm at the time of AVR conversion (116.6% of control), and peaking at 21.94 ± 0.4 cm (117.6% of control) at one week after initiation of reversed flow. At six weeks after AVR lower limb circumference had fallen to 20.29 ± 0.9 cm (108.8% of control) (Fig. 5).

Doppler ultrasonography documented femoral arterial flow through the venous anastomosis in each of six animals studied at the level of the stifle 3 weeks after surgery. In two animals an arterial pulse could be palpated manually in a dilated peripheral vein well beyond the stifle. Multiple large vascular collaterals developed subcutaneously (Fig. 6). Four months after surgery three animals were re-examined, and all were found to have a positive Doppler signal in the peripheral limb; one had a palpable pulse 15 cm below the level of AVR. The presence of Doppler signals in operated animals is recorded in Table 2.

Angiograms were performed at several times after operation. Examined serially, these demonstrate increasing arterial collateral ingrowth and, in several cases, persistent retrograde venous flow to the level of the ankle (Fig. 7). Graded collateral vessel formation is presented in Table 2. So far as could be determined, 14/19 animals had patent AV communications at 1 month, and 6/7 selected animals demonstrated angiographic patency at ten weeks after operation. No functional difference could be discerned between animals with and without patent AV anastomoses.

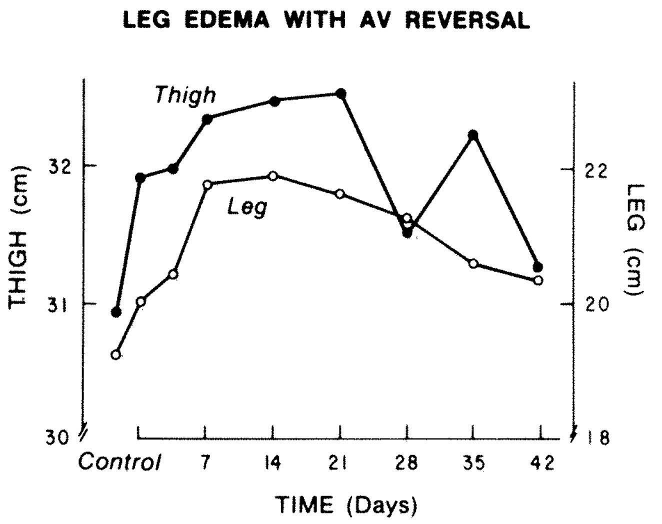


FIG. 5. With staged AV reversal (Group III), leg edema was modest and reversed within several weeks following second stage of operation.

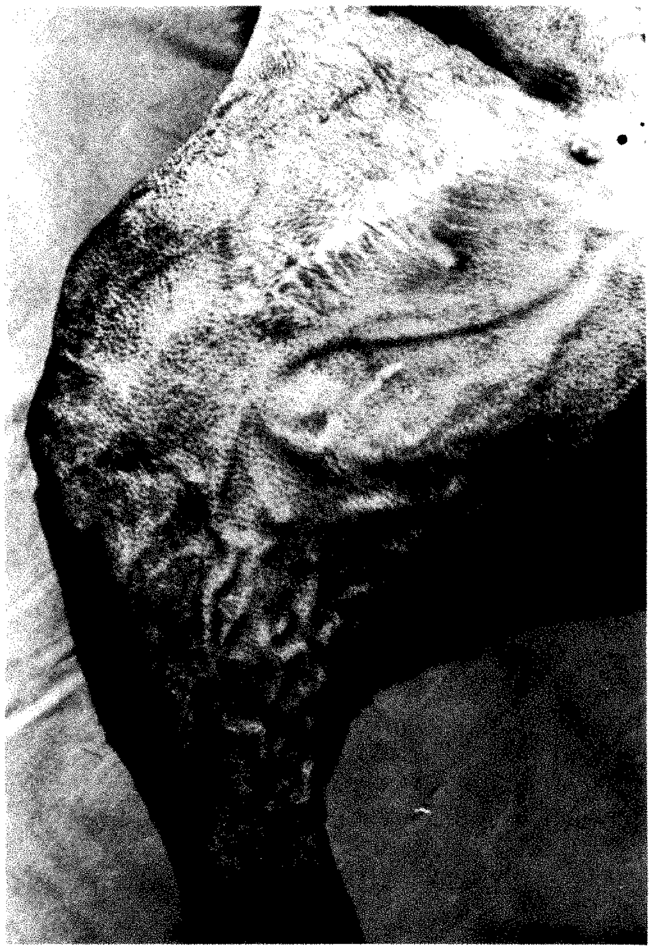


FIG. 6. Multiple subcutaneous vascular collaterals are easily visible in a Group III dog several months after AV reversal.

TABLE 2. *Cumulative Data for Group III Dogs, Staged AVR*

Dog No.	Circumferences C/c*						Doppler Pulses		AVR Patency by Angio.		Collaterals (0 to + + + +)
	Day 0	Day 3	Day 7	Day 14	Day 28	Day 42	3 Wk	16 Wk	4 Wk	10 Wk	
III-1	30/18	32/20	33/21	32/22	30/21	30/21	—	—	+	—	+ +
III-2	34/20	36/22	38/25	37/24	—	—	—	—	+	—	+ +
III-3	32/20	33/22	35/25	34/24	32/23	32/23	—	—	0	—	+ + +
III-4	30/17	32/20	32/21	32/21	32/21	32/20	—	—	+	0	+ +
III-5	28/15	29/16	29/19	29/19	29/19	—	—	—	0	—	+ + + +
III-6	30/19	31/19	31/22	30/21	—	—	+	+	+	+	+ +
III-7	30/20	32/22	32/24	32/23	32/22	31/20	+	+	+	+	+ +
III-8	29/17	30/18	30/21	30/20	29/30	—	—	—	0	—	+ + +
III-9	30/20	31/20	31/23	31/22	—	—	+	—	+	—	+
III-10	28/18	28/19	29/20	(29/20)†	—	—	—	—	—	—	—
III-11	30/18	30/19	31/22	31/22	30/22	—	+	—	+	+	+ +
III-12	34/20	35/21	37/22	37/23	35/22	—	—	—	+	—	+ +
III-13	28/15	—	29/16	—	—	30/16	+	—	+	+	+
III-14	30/20	31/21	31/23	31/22	31/21	—	—	—	+	+	+ +
III-15	34/20	35/21	34/22	35/23	34/23	33/22	+	+	+	—	+ +
III-16	30/18	30/18	30/19	31/20	—	—	—	—	0	—	+ + + +
III-17	32/19	34/20	34/22	34/21	33/21	—	—	—	+	+	+ +
III-18	35/21	35/22	35/24	—	—	—	—	—	0	—	+ + +
III-19	30/18	30/20	31/21	31/22	30/20	31/20	—	—	+	—	+ +
III-20	34/20	34/21	35/23	35/24	—	—	—	—	+	—	+
Mean C	30.90	32.00	32.35	32.47	31.50	31.29					
Mean c	18.65	20.05	21.75	21.44	21.25	20.29					
SEM	0.51	0.54	0.61	0.59	0.58	0.45					
SEM	0.23	0.38	0.50	0.36	0.37	0.90					
n	20	19	20	17	12	7					

* C, 10 cm above stifle; c, 5 cm below stifle.

† Animal found dead in cage: no cause for death found at necropsy.

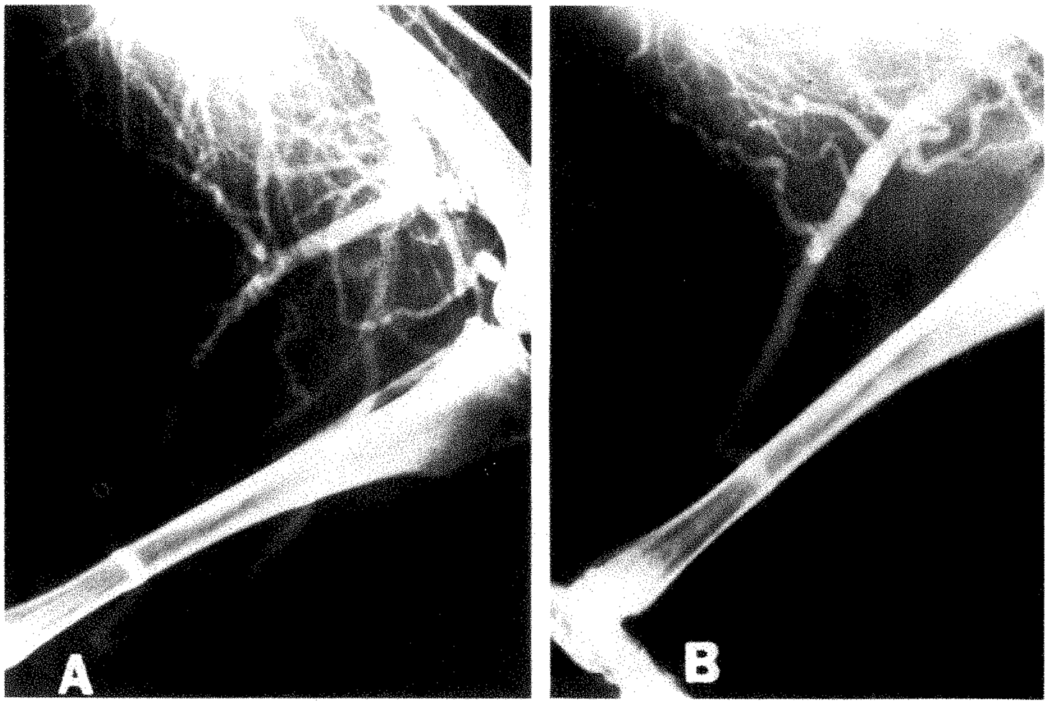


FIG. 7. Angiography in Group III dogs. (a, left) One week. (b, right) Six weeks. Note increase in collateral vessels over this period.

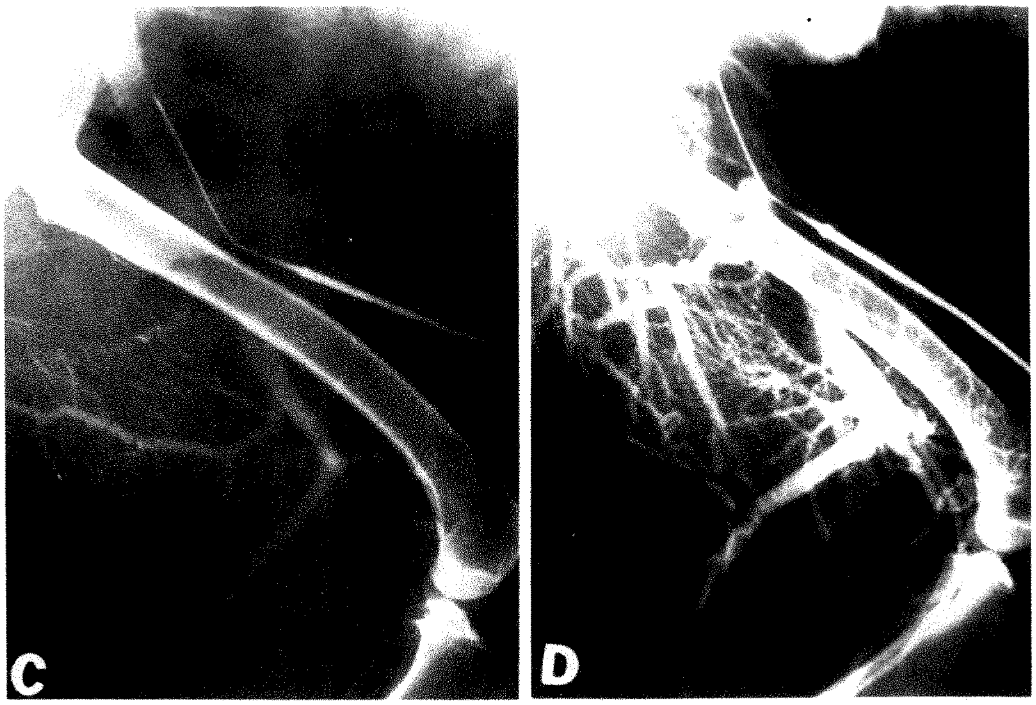


FIG. 7 c and d. Multiple films demonstrated persistent flow to level of the ankle.

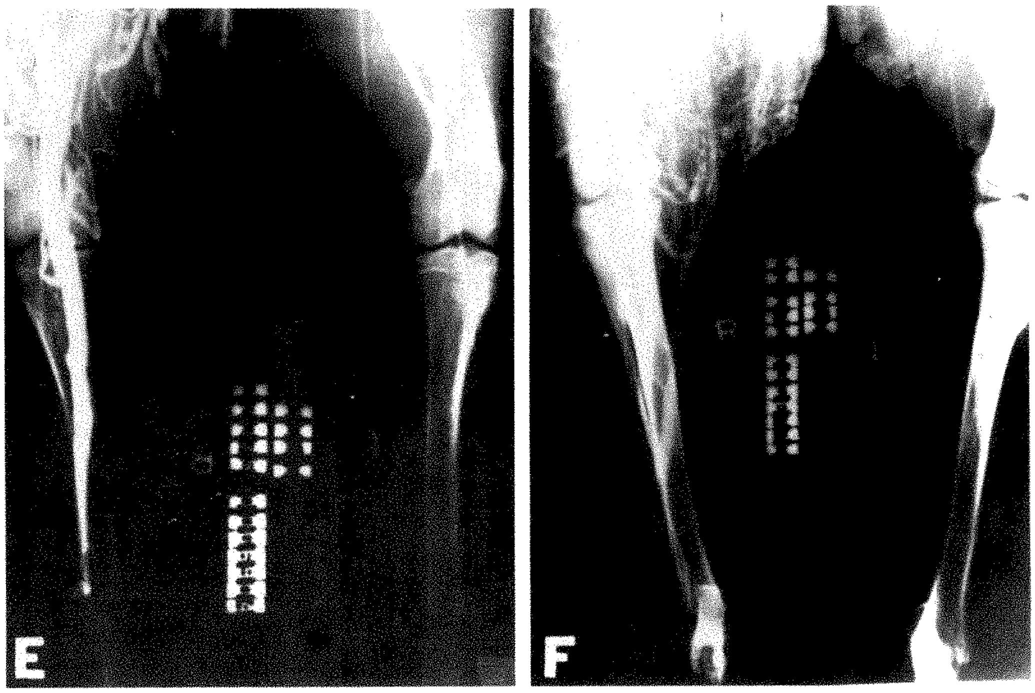


FIG. 7 e and f. Midstream aortograms demonstrate, by comparison with the non-operated left hindlimb, the massive increase in collateral vessels in both arterial and venous phases of the injections.

Electromagnetic flow determinations before and after the time of AVF formation, before and after AVR conversion, and one week after initiation of AVR in seven animals showed that initial (baseline) femoral artery flow was augmented by AVF formation, as expected. Initial moderate flows with AVR (87.2 ± 24.2 cc/min) rose to flows to 126.7 ± 48.3 cc/min one week later, as demonstrated in Figure 8 and Table 3.

Necropsy examinations showed no sign of cardiac chamber or wall hypertrophy; the pertinent vessels showed some evidence for thinning and tortuosity in the artery, while examination of the vein showed thickening of the intima and media with some fibrosis

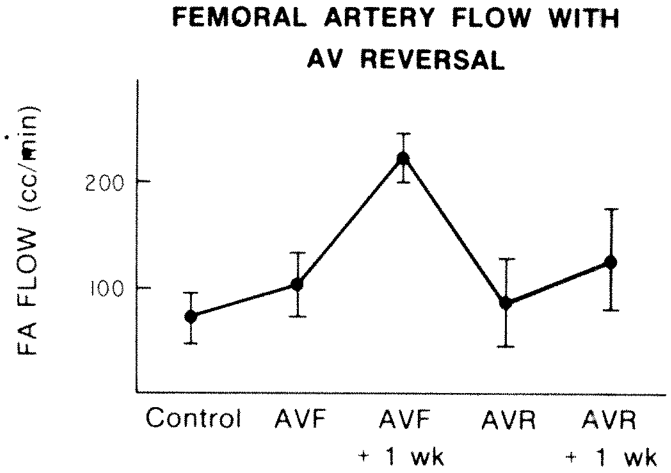


FIG. 8. Flow through femoral artery reaches a peak following AV fistula construction and decreases to control levels following proximal venous ligation and conversion of AV fistula to AV reversal.

(Fig. 9a). Serial excrescences in the vein were felt to represent thrombosed valves (Fig. 9b). No abnormalities were noted upon microscopic examination of the skin or muscle.

One dog was kept for 24 months after operation. Clinically the animal did well, without evidence for disability or exercise intolerance. The animal was then anesthetized and underwent angiography by techniques described previously. The angiogram (Fig. 10) shows thrombosis of the main AVR channel but profuse collateral flow through serpiginous parallel vessels. The animal was killed and multiple sections of vessels were taken for microscopic examination. As before, they demonstrated thrombosis of the valves and arterialization of the veins, with intimal and medial hypertrophy. The AV anastomosis showed an intimal ingrowth which had rendered it stenotic (2 mm) but not occluded.

In summary, heroic denuding of actual and potential collateral sources, both ipsilaterally and contralaterally, ultimately led to a canine surgical preparation that provided reproducible, irreversible limb ischemia and gangrene in seven animals (Group I). When immediate end-to-end femoral AVR was added to this preparation (Group II), massive incapacitating limb edema resulted, accompanied by incontrovertible signs of poor tissue perfusion and sepsis. However, when limb devascularization was accompanied by a side-to-side AVF, converted one week later to true AVR (Group III), all animals survived the procedure and 19/20 were electively killed up to 24 months later. None demonstrated significant limb edema and several clinical, physiologic, and angiographic measures suggested that adequate tissue perfusion was provided by AVR.

Discussion

There has been no shortage of innovative attempts to salvage ischemic extremities in circumstances in which standard revascularization procedures (endarterectomy, bypass grafting, sympathectomy) have failed. Direct muscle revascularization,[14] implantation of Ivalon sponge cubes into which the superior epigastric artery was inserted,[4] connection of the arterialized *in situ* saphenous vein into the medullary cavity of the femur,[16] and subcutaneous transfer of omental pedicle grafts[3] are among the more creative trials undertaken either in experimental animals or in patients.

That increased blood flow and intense collateral vessel formation occurs around an arteriovenous communication, either congenital or acquired, has led occasional investigators to explore the use of the AVF for tissue revascularization. Experimental studies in dogs by Root and Cruz[12] and in turkeys by Matolo et al.[11] suggested that an AVF can cause, both by retrograde venous flow and by intense arterial collateralization, perfusion sufficient to nourish an extremity. Pilot clinical studies between 1965 and 1970 by groups in San Francisco and Honolulu implied occasional successes in ameliorating limb ischemia, but these have not been confirmed subsequently. Similar studies with arteriovenous fistulas, without reversal, have also been recently reported from our laboratory.[5,6] In these experiments, AV fistula alone offered no protective physiologic benefit against a severe limb ischemia model, in marked contrast to the dramatic benefits to limb perfusion and tissue nutrition which followed the construction of an anastomosis with an AV reversal component. For this reason, and because of the relatively large literature confirming the absence of significant protection from acute ischemia associated with simple AV fistula construction, no "control" group of AV fistula animals was included in the current experimental series.

TABLE 3. *Electromagnetic Flow Data for Group III Dogs, Staged AVR*

	Electromagnetic Flow (ml/min)				
Dog No.	Control	AVF	AVF + 1 Wk	AVR	AVR + 1 Wk
III-25	68	62	160	38	—
III-26	52	88	225	60	95
III-27	112	162	420	180	205
III-28	75	88	180	80	—
III-29	98	148	—	—	—
III-30	66	90	205	45	80
III-31	48	98	165	120	—
Mean flow	74.1	105.1	225.8	87.2	126.7
SEM	9.5	14.7	43.9	24.2	48.3

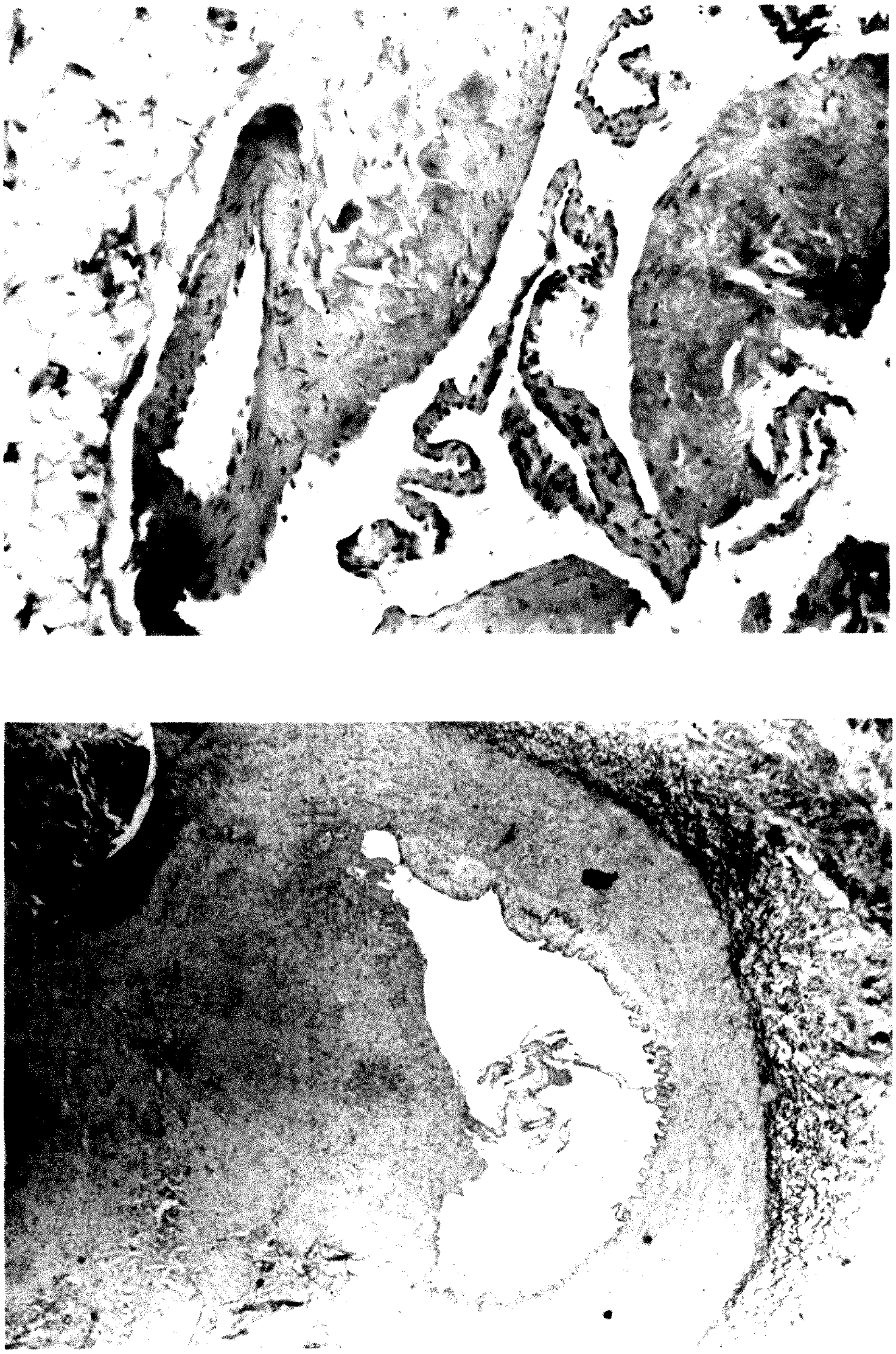


FIG. 9a and b. (a) Representative section of vein through which reversed arterial flow has passed 24 months in a Group III dog. The intima and media are significantly thickened. (b) Tangential section of venous valve in a 24-month-old Group III dog. The valve was markedly shortened and thickened and on gross examination of the vessel surface, the valve was clearly incompetent against reversed flow.

Flow reversal, perhaps the most radical revascularization concept of all, is also the oldest, predating the beginnings of vascular surgery. The concept was attempted experimentally in 1881, and the first clinical attempt, by the Spanish surgeon, San Martin y Satrustegui, occurred in 1902.[13] Occasional successes engendered enough enthusiasm that widespread clinical trials were carried out prior to 1920. Ultimately,

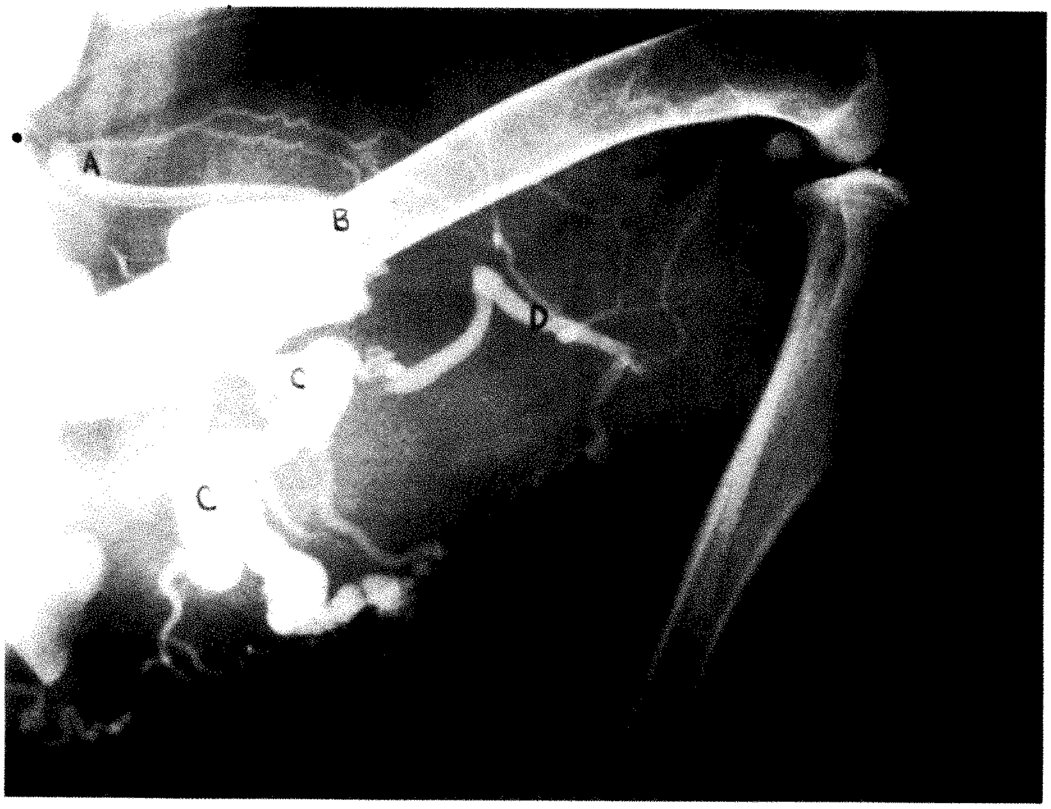


FIG. 10. Angiogram of Group III dog 24 months after AVR. A, site of femoral artery injection; B, site of AV anastomosis; C, massive venous collaterals; D, site of ongoing retrograde venous flow; E, new arterial collaterals.

however, the physiologic inconsistency of the theory and its poor results in practice were responsible for discarding the concept.

Spurred by the success of new attacks on congenital cardiac defects, Beck[2] developed several procedures involving retrograde perfusion of the myocardium via the cardiac veins in patients with coronary artery insufficiency. His coworkers[10] attempted to revascularize the cerebral circulation of patients suffering from cerebral palsy, mental retardation, or epilepsy by anastomosing the carotid artery to the jugular vein. At about the same time, Johnston et al.[9] reported good to excellent results in each of nine patients with threatened limb gangrene on whom they performed end-to-end femoral triangle AVR. However, in a careful clinical study of such centrally located AVRs. Szilagyi et al.[15] demonstrated rapid stepwise loss of the pressure head due to the succession of venous valves. Alternative bypass and endarterectomy techniques were developed, and vascular surgeons again lost interest in AVR.

More recently, Root and Cruz[12] demonstrated that tissue perfusion can be supplied by AVR in dogs. Those investigators, as well as Amir-Jahed[1] and Matolo et al.,[11] further showed that immediate end-to-end AVR is inevitably followed by a massive transudation of fluid and edema formation. Though his attempts were directed toward the amelioration of leg-length discrepancy rather than tissue revascularization, Hiertonn[8] demonstrated that formation first of an AVF, followed later by ligation of the central venous limb to yield a true AVR, provided an excellent result, with augmented leg length development and the absence of excessive edema formation. His experiments formed the basis of our two-staged approach.

It is extraordinarily difficult to produce limb gangrene in the dog, whose propensity to develop a new and major collateral supply from tiny remote arterial twigs is well recognized. Since the current investigation was designed to ascertain whether arterial flow retrograde in the veins would keep tissues alive, an extreme control preparation was required, *i.e.*, a limb with no other nutritional blood supply that inevitably would undergo ischemic necrosis without a further, successful, therapeutic maneuver. That the current Group I model is a satisfactory "ischemic limb" preparation is supported not only by this study's results, but also by comparison with the essentially identical Group I dogs of Root and Cruz[12] and Group I turkeys of Matolo et al.[11]

The simplest AVR (end-to-end connection of femoral artery and vein) caused severe limb edema and death in two-thirds of the animals. Thrombosis of the AVR was frequently demonstrable, in association with lethal limb gangrene. The staged AVR preparation, in which an initial side-to-side arteriovenous fistula was converted to AVR by ligation of the central venous limb, was very acceptable. Limb edema was not a prominent feature, and other clinical and quantitative criteria suggested that these devascularized limbs now had an adequate blood supply.

A number of "physiologic fallacies" have been presented as evidence against the usefulness of AVR in limb revascularization:

> 1) The flow must traverse competent venous valves. However, *in situ* saphenous vein femoral-popliteal grafts conduct similarly reversed flow following valve destruction.
>
> 2) Centripetal venous tributaries might shunt blood to the superficial venous system and decompress the inflow arterial pressure head, to the extent that little or no perfusion of the distal microcirculation would occur. However, the success of the Group III preparation speaks against this concern. Further, ligation of perforating veins connecting the deep and superficial venous systems could block such shunting, if necessary.
>
> 3) Can arterial blood presented retrograde to the terminal circulation carry out normal cellular nutrition and clearance of metabolites? Microvascular work by Zweifach[17] using vital dyes suggests that exchange of small molecules can occur with such reverse perfusion, and Heimbecker et al.[7] demonstrated oxygen uptake across a retroperfused capillary bed.
>
> 4) If the venous tree is used as inflow, what will serve as the venous outflow? In our preparation, the superficial venous tree is used as an inflow route. It is likely that new deep venous collaterals rapidly form and/or enlarge, as demonstrated by the Group III animals with ongoing arterial inflow (Fig. 8) in the absence of excessive edema formation (Fig. 5).

The current experimental thus has provided 1) a reproducible canine model for limb ischemia, 2) proof of unacceptably massive edema formation with immediate end-to-end AVR, and 3) evidence that conversion of an initial AVF into an AVR in a limb previously made irreversibly ischemic appears to salvage the limb without excessive edema formation. The concept of staged venous flow reversal therefore appears worthy of further investigation as an approach to the severely ischemic extremity.

Summary

Reversal of the circulation arises phoenix-like from the ashes of authoritative assertions of its inutility in the management of severe peripheral ischemia. The current study suggests that the excessive edema formation that occurs with immediate end-to-end AVR can be avoided by forming an initial end-artery-to-side-vein AVF, with later ligation of the central venous limb to cause AVR. Nineteen of 20 dogs enjoyed long-term survival with such a preparation. Several theoretical fallacies exist, asserting that AVR cannot perform retrograde perfusion of the terminal circulation. These issues can be only partially answered from the published reports and are under active investigation in our laboratory.

References

1. Amir-Jahed, A. K.: Revascularization of Lower Extremities by Reversal of Blood Flow with and without Lumbar Sympathectomy: An Experimental Study. Surgery, 59:243, 1966.
2. Beck, C. S.: Surgical Operations for Coronary Artery Disease. *In* Encyclopedia of Thoracic Surgery, Vol. II. Berlin, Springer-Verlag, 1959, p. 779.
3. Casten, D. F. and Alday, E. S.: Omental Transfer for Revascularization of the Extremities. Surg. Gynecol. Obstet., 126:301, 1971.
4. Friedman, E. W., Lambert, P. B. and Frank, H. A.: Vascular Connections Established by Arteries Implanted into the Lower Extremity with Plastic Sponge as an Intermediary. Surgery, 60:386, 1966.
5. Gausewitz, S., Gerard, D. F., Dilley, R. B. and Bernstein, E. F.: Arteriovenous Anastomosis (AVA) and Arteriovenous Fistula (AVF) in Revascularizing the Ischemic Canine Hindlimb. Surg. Forum, 29:211, 1978.
6. Gerard, D. F., Dilley, R. B. and Bernstein, E. F.: The Acute Physiologic Effects of an Arteriovenous Anastomosis in the Devascularized Canine Hindlimb. Surg. Forum, 28:206, 1977.
7. Heimbecker, P., Vivien, T. and Blalock, A.: Experimental Reversal of Capillary Flow. Circulation 4:116, 1951.
8. Hiertonn, T.: Arteriovenous Fistula for Discrepancy in Length of Lower Extremities. Acta Orthop. Scand., 31:25, 1961.
9. Johnston, C. G., Jordan, P. and Cloud, T.: Arteriovenous Anastomosis in Traumatic Vascular Lesions. Ann. J. Surg., 80:809, 1950.
10. McKhann, C. F., Belknap, W. D. and Beck, C. S.: Cervical Arteriovenous Anastomosis in Treatment of Mental Retardation, Convulsive Disorders, and Cerebral Spasticity. Ann. Surg., 132:162, 1950.
11. Matolo, N. M., Cohen, S. W. and Wolfman, E. F.: Use of an Arteriovenous Fistula for Treatment of Severely Ischemic Extremity: Experimental Evaluation. Ann. Surg., 184:622, 1976.
12. Root, H. D. and Cruz, A. B., Jr.: Effects of an Arteriovenous Fistula on the Devascularized Limb. JAMA, 191:109, 1965.
13. San Martin y Satrustegui, A.: Chirurgie de l'appareil Circulatoire: l'anastomose Artério-veineuse. Sem. Med., p. 395, 1902.
14. Shionoya, S., Ban, I. and Nakata, Y.: Skeletal Muscle Revascularization by Vascular Implantation. J. Cardiovasc. Surg., 14:208, 1973.
15. Szilagyi, D., Jay, G. D. and Munnell, E. D.: Femoral Arteriovenous Anastomosis in the Treatment of Occlusive Arterial Disease. Arch. Surg., 63:435, 1951.
16. Vetto, R. M. and Belzer, F. O.: Use of an Arterio-bone Fistula in Advanced Ischemia. Surg. Forum, 16:131, 1965.
17. Zweifach, B. W.: The Structural Basis of Permeability and Other Functions of Blood Capillaries. Cold Spring Harbor Symposia on Quantitative Biology, 18:216, 1940.

Minor Hemobilia

Clinical Significance and Pathophysiological Background

PHILIP SANDBLOM, M.D., VELIMIR MIRKOVITCH, M.D.

Profuse hemorrhage into the biliary tract—major hemobilia,—is an alarming condition which attracts much attention. Minor hemobilia, often caused by gallstones or operative injury, is much more frequent, yet often neglected. Clinical observations indicate that minor hemobilia is not always an innocent condition with the blood remaining fluid and unobtrusively flowing into the intestine. Examples are given where clots from occult hemobilia have caused diagnostic errors or obstructed the bile flow, thus imitating gallstones for which they may be mistaken. Experiments have been performed to elucidate the pathophysiology of this clot formation: 1) A model of the biliary tract was constructed with bile flowing through it. When blood was injected forcefully to simulate a major hemorrhage, mixed clots of blood and bile were formed. When introduced gently, as in minor hemobilia, the blood flowed immiscibly to the lowest level where it formed a clot of pure blood. The clots dissolved under the influence of flowing bile, but remained intact when protected from the flow. 2) Mixed clots were mushy and dissolved spontaneously, while pure clots remained solid and stable. When clots containing increasing amounts of bile were incubated, increasing amounts of cleavage products of fibrinogen and fibrin were formed. 3) Blood clots were produced in gallbladders of 33 dogs. Pure clots remained solid and floating while mixed clots formed a mushy layer, strongly adherent to the mucosa. Both kinds of clots disappeared after two–four weeks, but remained if bile flow was diverted. These findings explain why under certain circumstances minor hemobilia acquires clinical significance by forming clots that may obstruct the flow or cause diagnostic errors. Successful dissolution of "retained stones" may occasionally have the simple explanation that blood clots, mistaken for calculi, have been fibrinolysed. Consequently, in biliary obstruction or when defects are found on cholangiography, the possibility of blood clots in the ducts should be considered even in the absence of overt gastrointestinal hemorrhage.

From the Department of Surgery and the Department of Experimental Surgery, C.H.U.V., University of Lausanne, Switzerland

MINOR OR OCCULT HEMOBILIA has attracted far less attention than major hemobilia in spite of its much greater frequency. The reason is probably that insignificant bleeding into the biliary tract may pass unnoticed, whereas massive hemorrhage will often cause alarming symptoms demanding urgent diagnosis and treatment.

It is true that before the era of cholecystography, the finding of occult blood in stools following biliary colic was a sign of some importance in the diagnosis of gallstones, but since then the subject of minor hemobilia has been neglected.

In a previous work on the formation of clots in the biliary tract,[22] we observed that even in experiments imitating minor hemorrhage the blood coagulates, and that these clots are different from those arising in major hemobilia. This finding and a number of clinical cases that we have observed and found in the literature convinced us that minor hemobilia is not always innocent, with the blood unobtrusively flowing into the intestine, but may be of clinical significance through clot formation in the ducts.

The purpose of this paper is to describe a few typical cases, illustrating the different clinical manifestations of the syndrome and to report on a further series of experiments where we have examined what happens when a small amount of blood enters into the bile stream.

Clinical Features

By minor hemobilia we understand biliary tract hemorrhage which is not accompanied by overt gastrointestinal bleeding. As most cases of this kind are not reported, it is impossible to know their actual frequency. We are, however, well informed about two etiologic groups, namely those caused by gallstones and by liver puncture. In 1892, Naunyn[13] observed the frequent occurrence of biliary tract hemorrhage in gallstone disease. In a prospective study, Gad[6] found

---

Reprint requests: Philip Sandblom, Department of Surgery, C.H.U.V., University of Lausanne, Switzerland.

0003-4932/79/0800/0254$01.05 © J. B. Lippincott Company

occult melena in 25% of 238 cases with stones in the gallbladder and in 37% of 96 cases with stones in the common duct. Occult melena has been reported in between 3[3,26] and 7%[1] of cases after liver puncture. After biliary surgery one often sees blood-tinged bile in the T-tube; Hepp[7] even recommends the use of this occurrence to direct postoperative anticoagulant therapy.

Occult hemobilia is thus a very common condition. In contrast, the proportion of cases which present symptoms other than microscopic bleeding is small indeed. In a series of 355 well-investigated cases of hemobilia, compiled from the world literature,[20] only 10% presented biliary symptoms without concomitant macroscopic gastrointestinal hemorrhage.

Case Reports

The symptomatic cases are found in different etiologic groups as exemplified in the following case histories:

From Trauma

Case 1 (Räf[19]). A young woman received 20 stabwounds in the abdomen from her husband. At emergency operation, perforating lesions of the left liver lobe were repaired. From the fifth postoperative day onward, there were signs of obstructive jaundice with serum bilirubin rising above 20 mg/dl. Traumatic hemobilia was suspected and the patient was reoperated. Following opening of the common duct, several organized blood clots, about 10 cm in length, representing casts of the ducts, were found; even the entrance of the Duct of Wirsung was visible (Fig. 1).

Comment. This case as well as Cases 6, 7 and 8 illustrates the fact that a solid clot alone suffices to cause a total obstruction of the bile flow.

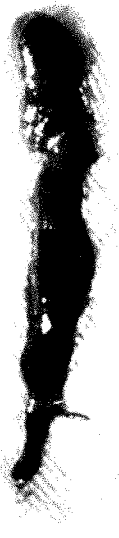


FIG. 1. Case 1. A blood clot extracted from the common duct in a case of traumatic hemobilia. Note the protuberance, probably a cast of the distal end of the pancreatic duct. Actual size. (Räf, Serafimerlasarettet, Stockholm).

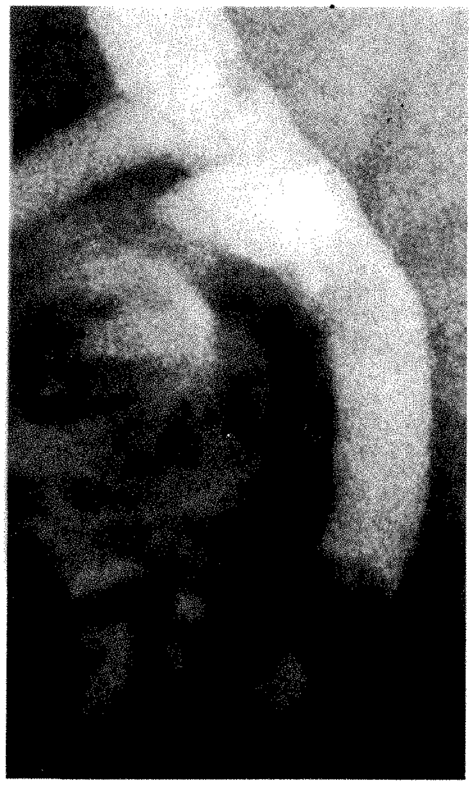


FIG. 2. Case 3. Cholangiogram three weeks after choledocholithotomy. A defect thought to represent a remaining stone is observed; at relaparotomy a blood clot corresponding to the defect was extracted, whereupon repeated cholangiogram was normal. (Surgical Department, CHUV, Lausanne).

During Operation

Case 2 (Sandblom[22]). Three stones were extracted from a dilated common duct with some difficulty but without any disturbing bleeding. Repeated peroperative cholangiograms showed a filling defect, which was suspected of representing a remaining stone. On reopening the duct, it was shown to be due to a fresh coagulum.

Comment. This kind of event is not uncommon. Many of our surgical friends have told us of analogous experiences.[11]

Soon After Operation

Case 3 (Sandblom[21]). A common duct stone was extracted. Cholangiogram showed free passage and no sign of overlooked stones. A T-tube drained clear bile for three weeks. At this time a cholangiogram showed a large filling defect, which was interpreted as a remaining stone (Fig. 2). At operation, however, it turned out that the defect was caused by a blood clot.

Comment. Imagine the nice success one would have had with perfusion dissolution of this "stone!" Millbourn[11] and Schein[24] among others have shown similar pictures.

Late After Operation

Case 4 (Svane[25]). The patient died from complications of obstructive jaundice that had increased during three weeks. Cholecystectomy had been performed ten months prior to death. The pathologist found a 20 × 10 mm blood thrombus obstructing the common duct and firmly attached to the duct wall. Remnants of silk that were found in the thrombus were supposed to have migrated through the duct wall, causing inflammation, bleeding and clotting. No gastrointestinal bleeding had been noticed until the day of death.

Comment. The fact that the thrombus was built up of an older, mural part superimposed with fresh desposits indicate that the hemobilia had lasted for some time.

After Liver Puncture

Case 5A. (Nakayama[12]). A patient with obstructive jaundice had a percutaneous transhepatic cholangiography which revealed a very dilated biliary tract and complete occlusion of the common duct. After the liver puncture, the radiograms showed blood coagula in the right hepatic duct. Minor hemobilia continued and ten days later renewed cholangiography revealed huge blood coagula which almost completely filled the biliary tract (Fig. 3A). Simultaneously the bile flow from the drainage tube became minimal. Urokinase was instilled and the next day the coagula had disappeared and the outflow of bile was resumed.

Comment. The increase in the size of the coagula was probably due to persistent bleeding and a concomitant lack of fibrinolysis through the cessation of bile production. The clot finally had to be dissolved with the help of a fibrinolytic agent. This contrasts with a case of ours,[22] Case 5B, where the bleeding was transitory.

Case 5B. Half an hour after liver puncture, the radiograms showed a distally impacted common duct stone and a 4 cm long filling defect in an hepatic duct, first reported by the radiologist as being due to stones (Fig. 3B). At operation the following day, it was evident that this defect had been caused by a coagulum, of which only small red flakes remained.

Comment. The case illustrates how quickly a coagulum can form in the biliary tract; also how rapidly it may dissolve. Cahow[3] relates the bleeding tendency after transhepatic cholangiography to the distension of the ducts.

From Gallstones

Case 6 (Sandblom). An elderly woman had a three-day history of biliary colic, obstructive jaundice, chills and fever. An abdominal CT scan (Fig. 4A and B) indicates a dilated biliary tract, a large common duct stone and suspected stones in the cystic duct. At operation there were acute inflammatory changes around the gallbladder and extrahepatic ducts. A round stone was located in the confluence of the cystic duct and the hepatic duct. Two large, very firm blood clots were occluding the common duct (Fig. 4C). At histologic

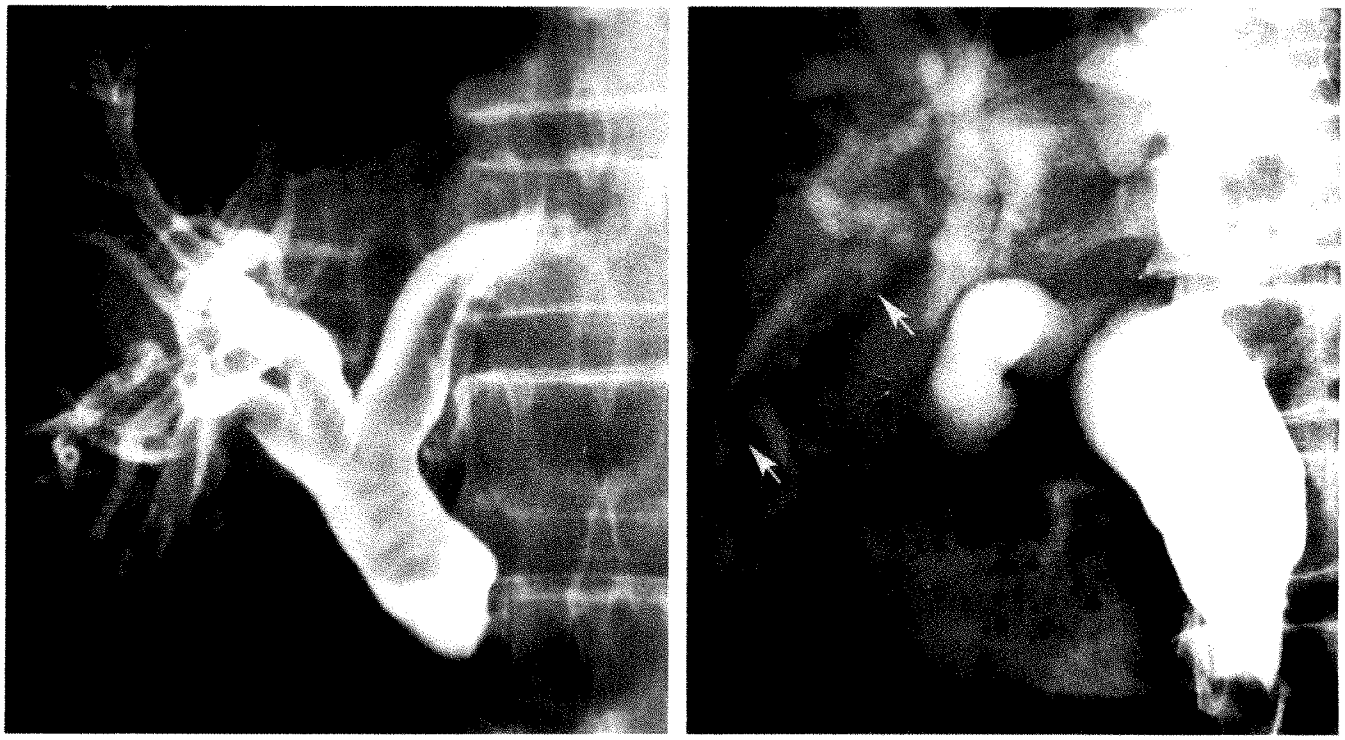


FIG. 3. Case 5A. Clots produced by percutaneous transhepatic cholangiography. (A) Continuous minor hemobilia for ten days after liver puncture in a case of pancreatic carcinoma produced huge blood coagula almost completely filling the biliary tract. The coagula dissolved completely within 24 hours after instillation of Urokinase through the transhepatic drain. (Nakayama, Kyushu University, Fukuoka). (B) Case 5B. Cholangiogram half an hour after liver puncture showed an impacted stone at the ampulla and a 4 cm long defect in a bile duct (between the arrows), first thought by the radiologist to represent stones, but found to be caused by a coagulum. At operation the next day it was noted that the coagulum had been nearly totally dissolved. (Veterans' Administration Hospital, San Diego).

examination they were noted to contain desquamated epithelium and mucus as sign of acute cholangitis.

Comment. The stone in the cystic duct had evidently eroded the inflamed mucosa of the biliary tract, causing minor hemorrhage with blood clots which obstructed the bile flow. It was the image of these coagula on the CT scan that was misinterpreted as a large choledochal stone.

In a similar case reported by van der Linden[10] the stones acted from a distance—they were located in the gallbladder where the hemorrhage originated to form an obstructing clot in the lower common duct.

From Cholangitis

Case 7 (Quast[18]). A 45-year-old man was admitted with signs of acute cholecystitis and moderate jaundice. After a week of improvement he suddenly had a relapse with severe biliary colic and rapidly increasing obstructive jaundice. He underwent surgery for suspected common duct stones and cholangitis. An inflamed gallbladder with pericholecystitis was encountered. Cholangiography showed a common duct of normal size but no filling of the hepatic ducts. The common duct contained infected bile but also a solid blood clot which presented as a Y-shaped cast of both hepatic ducts and the common duct down to the entrance of the cystic duct (Fig. 5). There were no stones anywhere and no blood in the gallbladder. The patient recovered.

From Liver Tumor

Case 8 (Johns[8]). A man, aged 70, was admitted with a one month history of epigastric colicky pain and increasing obstructive jaundice. Stool examination for occult blood was negative. He underwent surgery for suspected cancer in the head of the pancreas. A liver cell carcinoma was found in the right lobe of the liver. The common hepatic duct was enormously dilated as far as a point just above the junction of the cystic duct with the common duct.

The common duct was opened and a darkish-brown blood cast of the common, right and left hepatic ducts was found (Fig. 6). The pathologist discovered malignant tumor cells in the clot. The patient followed a downhill course and died three months later. Fisher and Creed[5] described a very similar case.

Pathophysiologic Background

In all these patients, the clinical signs were related to clot formation in the ducts. It is thus evident that the blood may coagulate even in minor hemobilia. Considering the high frequency of such bleeding in the biliary tract, one wonders why so few cases become symptomatic.

A better understanding of the pathophysiology should help to answer this question and might also aid in the prevention, diagnosis and treatment.

For this purpose we have conducted a series of experiments:

1) Injection of blood in various ways into an experimental model of the biliary tract containing flowing bile to study the formation of coagula.
2) Production *in vitro* of blood clots containing various proportions of bile in order to study their physical characteristics.

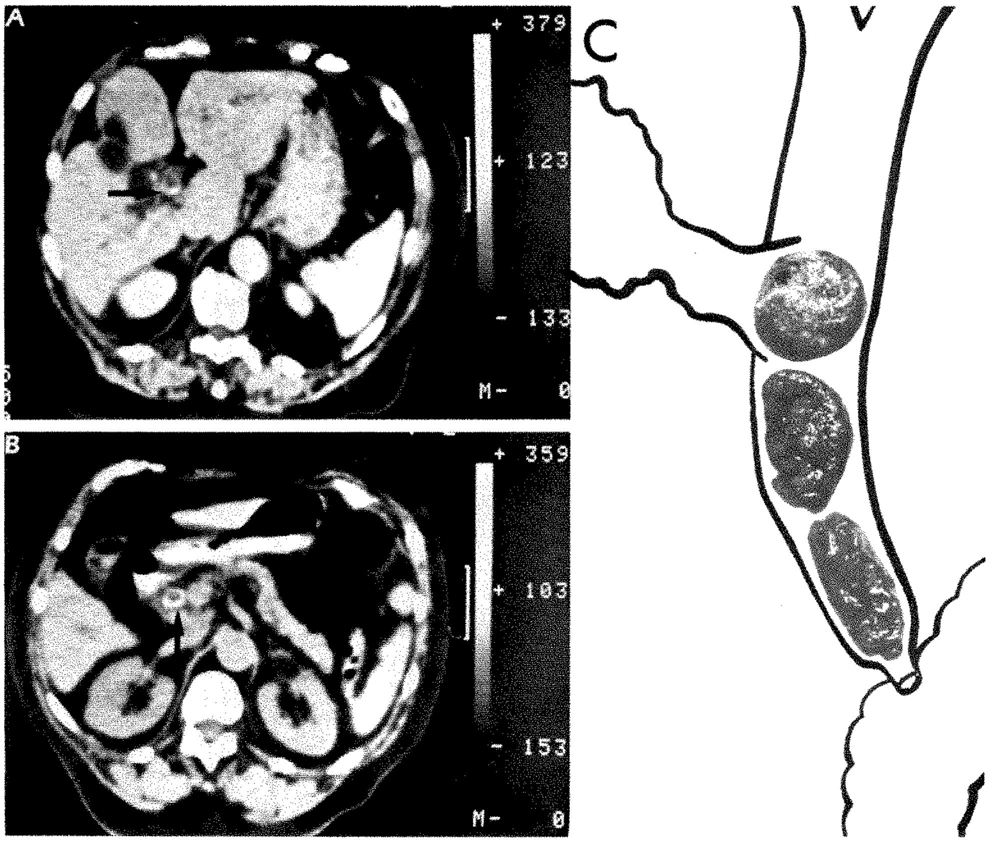


FIG. 4. Case 6. Clots produced by gallstones. Preoperative CT-scan. (Prof. Candardjis, Department of Radiology, CHUV, Lausanne). (A) At the level of the gallbladder there is a shadow (arrow) thought to represent a stone in the cystic duct. (B) At a lower level, showing the pancreas, there is a shadow (arrow) thought to represent a large gallstone in the common duct. (C) Drawing of the operative finding with photographs of the stone eroding through the cystic duct into the common duct and two occluding firm blood clots distally. These latter caused the shadow, misinterpreted as being caused by a gallstone in the common duct on the CT-scan. (Surgical Department, CHUV, Lausanne).

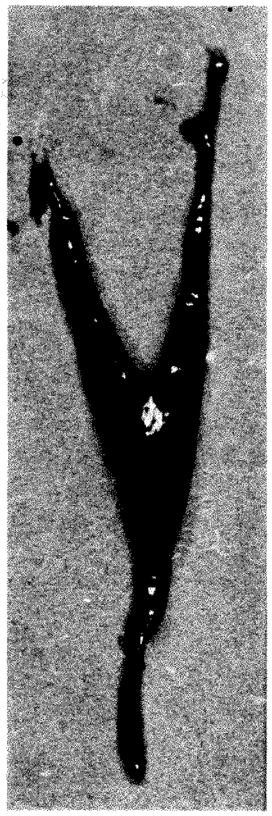


FIG. 5. Case 7. This Y-shaped blood clot is a cast of the right, left and common ducts down to the entrance of the cystic duct in a case of cholangitis. (Quast, Bezirkskrankenhaus St. Georg, Leipzig Zbl. Chir. 96: 601, 1971).

3) Injection of blood in various ways into the gallbladder of living dogs to compare the formation and fate of blood clots from slow and from profuse hemorrhage.

Model Experiments

A model of the extrahepatic biliary tract, previously described in detail,[22] was constructed and bile was made to flow through it. In a series of nine experiments, blood was injected either forcefully or gently. When injected forcefully to imitate a major hemorrhage (Fig. 7A), the blood partly mixed with the bile and formed soft, mushy clots, containing varying amounts of bile. When injected gently (Fig. 7B), it flowed immiscibly to the bottom of the system where it formed a solid clot of pure blood. When the clots were subjected to flowing bile, they were promptly lysed; when protected from the bile by diversion of the flow, they remained intact.

Studies of Mixed Clots of Blood and Bile in Vitro

With the finding that minor hemobilia produces pure blood clots whereas profuse hemobilia also gives rise to clots mixed with bile, it was considered interesting to study *in vitro* the characteristics of clots containing varying amounts of bile in comparison with pure clots and clots containing saline.

Materials and Methods. Sterile plastic test tubes of 10 ml, physiological saline solution, freshly drawn human blood and fresh human hepatic bile were used.

Nine tubes were set up and 2 ml of blood were poured into each. Tube 1 had only pure blood. In tubes 2 and 3, the blood was allowed to flow down through and remain under a layer of 2 ml saline or bile respectively. In tube 4, blood and saline were mixed in a proportion of 80:20 (v/v) and in tube 5 a similar mixture of blood and bile was prepared. In tubes 6 and 7, the proportions were changed to 60:40 (v/v) blood: saline or bile and in tubes 8 and 9 to 50:50 (v/v) blood: saline or bile respectively.

After 30 minutes and, again, after four hours of incubation in a humid chamber at 37°, the clots and the supernatant that had separated were examined. The clots were measured after the four hour incubation to reveal the effect of contraction and/or fibrinolysis, and the supernatant was analysed for cleavage products of fibrinogen and fibrin. Of three methods tried, namely: the staphylococcal clumping test, the Elcothrombotest and the immunochemical technique[16] using the specific cleavage-associated neoantigens, we settled for the latter as being the most accurate.

Results: Table 1 and Fig. 8). The blood coagulated in all the tubes. The clots subsequently diminished in size. Pure clots (1, 2 and 3) and those mixed with saline (4, 6 and 8) were solid and produced a clear supernatant. Those mixed with bile (5, 7 and 9) were larger, soft to mushy, diminished less in size and liquefied to greater degrees with increasing proportions of bile. Their supernatant was dark red.

The amounts of cleavage fragments of fibrinogen

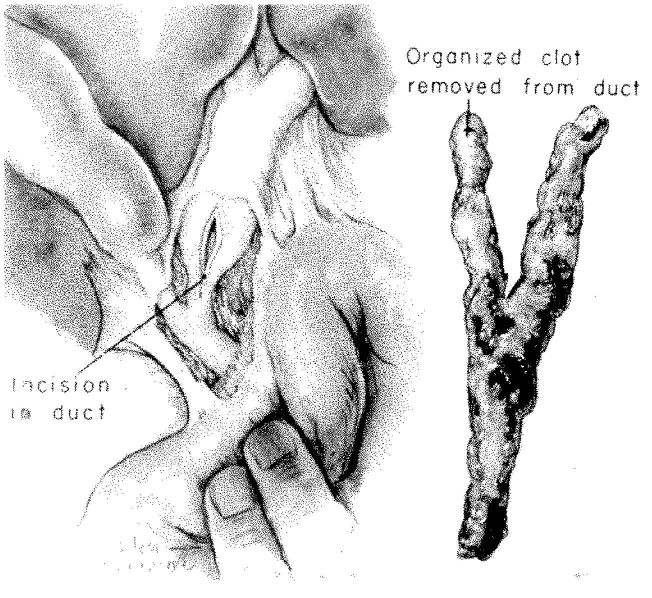


FIG. 6. Case 8. An occluding clot caused by minor hemobilia from liver tumor; malignant cells were embedded in the clot. (Johns, Johnston-Willis Hospital, Richmond, Virginia. Ann. Surg., 153: 706, 1961).

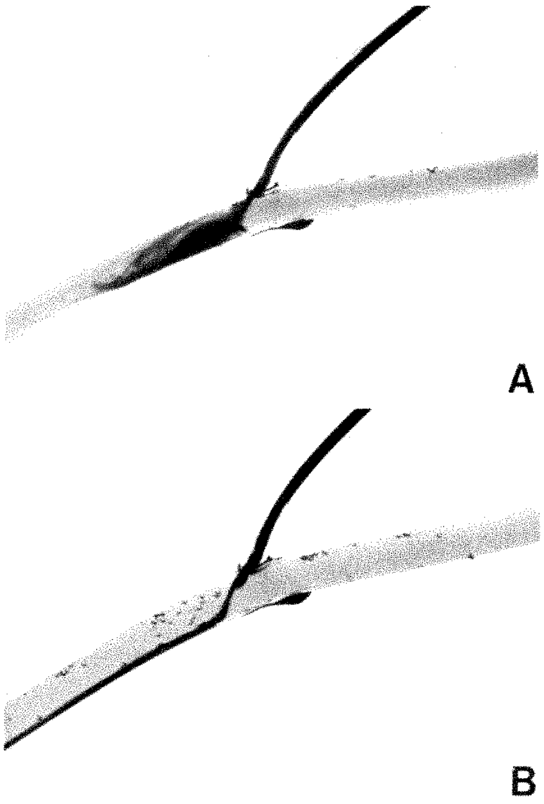


FIG. 7. Detail of a polyvinyl chloride tubing model of the extrahepatic bile ducts. Blood is injected into bile streaming through the system. (A) When injected forcefully to imitate major hemobilia, it causes turbulence and mixes with the bile. (B) When injected gently to imitate minor hemobilia, it flows immiscibly to the lower portion and forms a pure coagulum.[22]

and fibrin produced by the clots are given in Table #1. The supernatant of the clot that had formed under bile contained twice as much as the supernatant from pure blood. The same amount of split products was formed by the clot mixed with 20% bile, while the clots with 40 and 50% bile produced 5 and 6 times this amount respectively. None of the clots mixed with saline produced measurable amounts.

Comment. The diminution in size of those clots where the supernatant remained clear and contained only a small amount of fibrin split products was supposedly due to contraction, while in those where the supernatant became hemolysed and rich in split products, it was probably caused mainly by fibrinolysis. Thus, clots that were pure or merely mixed with saline contracted normally while those mixed with bile liquefied instead of contracting.

It is remarkable that even the blood mixed with 50% bile coagulated (30% had formerly been given as the limit[20]). This clot, however, was extremely fragile and it liquefied almost entirely during the incubation.

Animal Experiments

We now considered it timely to control our findings in living animals. An experiment was designed to compare the formation and fate of pure and of bile-mixed blood clots within the gallbladder.

Method. A series of 33 mongrel dogs were operated, the first one providing a pilot experiment to work out a suitable technique which turned out to be the following: Through a midline incision, the cystic duct was clamped. A blunt cannula was introduced through the fundus of the gallbladder to the bottom of the infundibulum and about half the content of the bile (4–15 ml) was evacuated. Blood was withdrawn from the vena cava. In half of the experiments, 4 ml of pure blood were slowly injected during 3–4 minutes, corresponding to a slow hemorrhage, while in the other half, 4 ml of blood were mixed with 1 ml of bile and the 20% mixture was injected somewhat faster (during 1 minute), corresponding to a more profuse hemorrhage where the blood mixes with the bile. The cystic duct clamp was not removed until 30 minutes later to allow time for clotting.

TABLE 1. *Nature and Behaviour of Blood Clots Mixed with Bile in Comparison to Pure Clots and Clots Mixed with Saline*

	Tube 1	Tube 2	Tube 3	Tube 4	Tube 5	Tube 6	Tube 7	Tube 8	Tube 9
Specimen	Pure blood	A layer of pure blood beneath an equal amount of saline	A layer of pure blood beneath an equal amount of bile	Blood mixed with 20% saline	Blood mixed with 20% bile	Blood mixed with 40% saline	Blood mixed with 40% bile	Blood mixed with 50% saline	Blood mixed with 50% bile
Nature and size of clot after 30 minutes	Solid 14 × 6 mm	Solid 15 × 7 mm	Solid 15 × 8 mm	Solid 18 × 6 mm	Soft 20 × 7 mm	Solid 21 × 5 mm	Very soft 29 × 10 mm	Solid 25 × 5 mm	Very soft 28 × 10 mm
After 4 hrs incubation in 37° humid chamber	Solid 13 × 7 mm	Solid 15 × 7 mm	Solid 13 × 7 mm	Solid 15 × 6 mm	Soft 19 × 5 mm	Solid 18 × 5 mm	Extremely soft 29 × 9 mm	Solid 21 × 6 mm	Liquefying 27 × 10 mm
Cleavage products of fibrinogen/fibrin molar concentration p-moles/ml	1.7	<1	4.0	<1	1.9	<1	10.4	<1	11.6

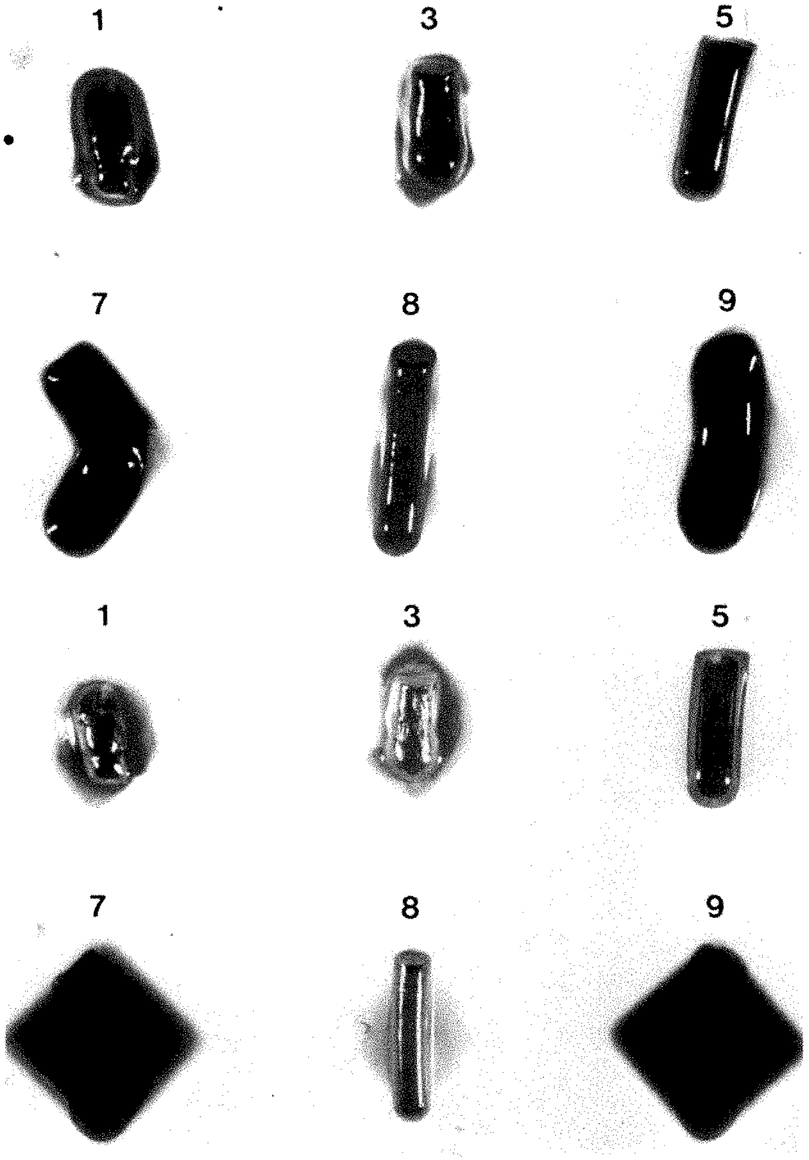


FIG. 8. Formation and fate of coagula in mixture of blood and bile or saline. Each clot is derived from 2 ml of blood with different amounts of saline or bile. (Top) 1—Pure blood. 3—Pure blood, coagulated under a layer of bile. 5—Mixed with 20% bile. 7—Mixed with 40% bile. 8—Mixed with 50% saline. 9—Mixed with 50% bile. The clots containing bile were larger and softer than the corresponding ones with saline. (Bottom) The same clots after four hours incubation in 37° humid chamber. The clots mixed with bile (5, 7 and 9) contract less and become mushy; they liquefy with increasing proportion of bile. The difference between contracting and liquefying clots is most evident in 8 and 9 respectively.

Cholecystectomy was performed after 30 minutes, 1 hour, 4 hours, 24 hours, one, two and four weeks. The gallbladder was opened, the contents were examined, and the mucosa was explored histologically.

Results. During the first 24 hours, the results were consistent. When pure blood had been injected slowly, there was a free floating firm clot, about 2 × 1 cm in size, formed as a cast of the infundibulum with a flat surface towards the fundus, which contained yellow bile (Fig. 9A). The mucosa adjacent to the clot was reddened, the rest being pale.

When a mixture of four parts of blood and one part bile had been injected quickly there was no formed clot but the mucosa was covered with a layer, 1–2 mm thick, of soft and smeary coagulum, adhering to the mucosa (Fig. 9B). When the specimen had been fixed, this layer peeled off easily.

During the following weeks the difference between pure and mixed clots was less pronounced. The clots became soft, gelatinous and lighter in color, and the yellow bile contained numerous black flakes, the size of a pinhead. After 2 weeks there were numerous small fragments and after 4 weeks half of the clots, whether pure or mixed, had vanished.

Considering that the diminution and disappearance of the clots was probably due to lysis by the flowing bile, we then performed an experiment where the two kinds of clot were kept for one week in gallbladders with the cystic duct ligated, *i.e.* in "excluded gallbladders." The clots now remained unaltered, both attached to the mucosa. The pure one was easily loosened but the mixed one could only be scraped off with difficulty.

A further experiment was performed where the outflow tract was left open in order to ensure free outlet for the blood in the absence of circulating bile, a situation often encountered in clinical practice when there is a nonfunctioning gallbladder. For this purpose, we ligated the hepatic ducts above the cystic duct before injecting the blood into the gallbladder. After a week we found that the pure clot remained and had turned into several pieces of very solid black material (Fig. 10A). There was not much left of the mixed clot (Fig. 10B). After two weeks the findings were again inconsistent; some clots, whether pure or mixed, were gone, some remained.

Histology

Method. The specimens for histologic study were fixed in 10% buffered formalin and embedded in paraffin. They were cut at 5 μm thicknesses and stained with hematoxylin and eosin. Some of the material was also colored with the Prussian blue stain for iron pigments and with Masson's trichrome stain.

Results. The histologic findings vary from one animal to another within each group. Slight alterations of the gallbladder mucosa are seen, particularly in the groups killed after four hours. These changes consist of flattening of the mucosal folds, swollen, pale-staining epithelial cells, some of which have lost their nuclei (ghost cells), edema of the perimuscular layer and an acute inflammatory infiltration. Mitoses were visible in the epithelia of some animals. Although these findings are slight, the impression is that those produced by a mixed clot are relatively more pronounced.

As the time of exposure of the mucosa to the clots increases, the differences in the histologic structure of the two groups are less evident. The mucosa becomes increasingly flattened in time, the perimuscular edema disappears and the inflammatory infiltration passes from subacute to chronic. At 14 days' exposure, fibrosis starts to appear as confirmed by Masson's trichrome stain. This fibrosis is especially dense in the perimuscular layer. After 28 days' exposure, fibrosis is more important. The Prussian blue stain was negative for iron pigments. There is no clear histological difference between the two types of blood clots in the 14 and 28 day groups.

Comment

As in the experiments *in vitro*, there was a great difference during the first 24 hours in the quality of pure clots and those mixed with bile. Their further development was related to the bile flow. When this was free, the clots, whether pure or mixed, diminished or disappeared within four weeks. When the flow on the contrary was totally interrupted both kinds of clots remained intact. The variation in longevity of clots during an intermediary stage, when the inflow of bile was interrupted but the outflow kept open suggests the possibility that the biliary tract mucosa also produces fibrinolytic activity.

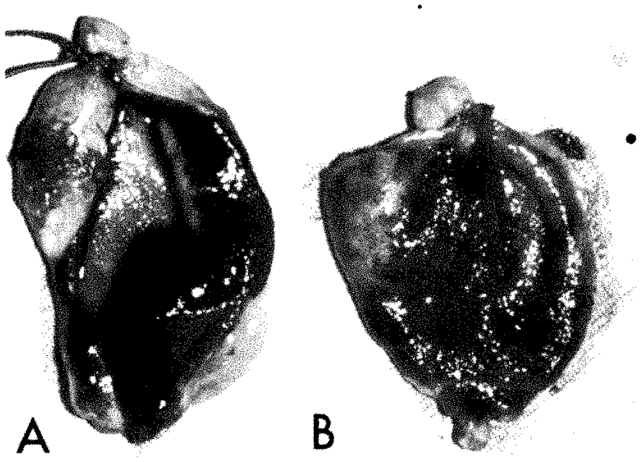


FIG. 9. Clots produced in gallbladders of dogs. Cholecystectomy after four hours. (A) A pure clot is solid and does not adhere to the reddened mucosa. (B) A mixed clot consists of a thin layer of smeary material, very adherent to discolored mucosa.

The animal experiments disclosed another difference between pure and mixed clots. Slow hemorrhage into the gallbladder where the blood does not mix with the bile resulted in solid, free floating clots. Profuse hemorrhage where the blood mixed with the bile, produced a clotted, strongly adherent layer on the surface of the mucosa; the attachment resembled that of a thrombus to the vessel wall. As the histology of the gallbladder mucosa was distorted very little and reacted only slightly differently to the two forms of clot,

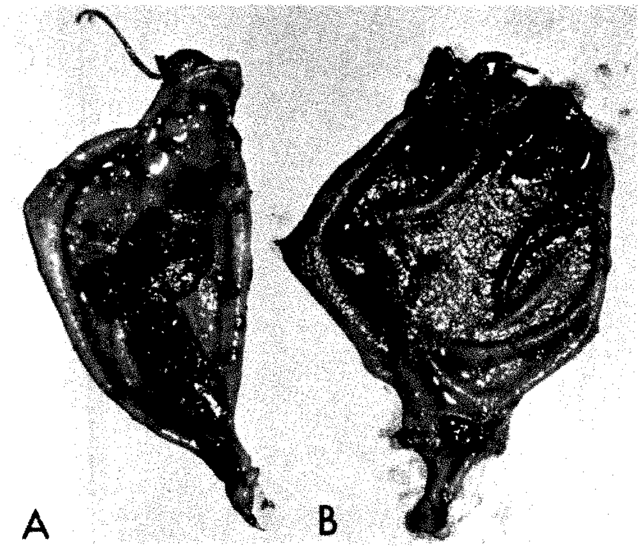


FIG. 10. Clots in "nonfunctioning" gallbladders, *i.e.* with outflow tract open in the absence of circulating bile. Cholecystectomy after one week. (A) The pure clot remains in several pieces of solid black material. (B) The mixed clot consists of pea-sized morsels clinging to the mucosa of the fundus and a 2 cm long string, partly attached to reddened mucosa.

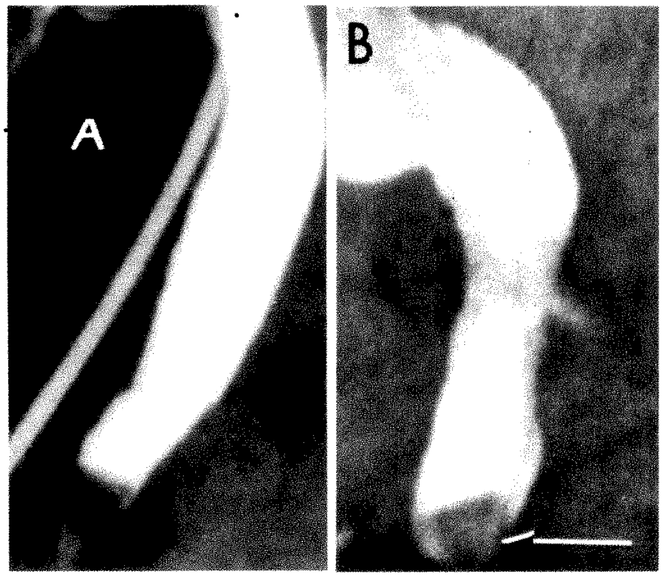


FIG. 11. T-tube cholangiogram defects of disputable origin. Although interpreted as being due to stones, they were probably caused by blood or blood clots. (A) A defect is seen at the lower end of the common duct. It disappeared after three washouts during one week with normal saline and lignocaine. The defect looks like a cast of the lower part of the common duct and probably represents a coagulum. (Catt, Princess Alexandra Hospital, Brisbane/Australia. Ann. Surg. 180:247, 1974). (B) The defect seen at the distal end of the common duct did not appear on a renewed cholangiogram 10 days later when the t-tube had been clamped. A stone of this size rarely passes spontaneously while a blood clot could well have been lysed by the bile flow after clamping of the tube. The upper oblique surface could be explained by the patient's position during coagulation. (Schein, Montefiore Hospital, Bronx/N.Y. Postcholecystectomy Syndromes. New York, Harper and Row, 1978).

the difference in the interaction between clot and mucosa is probably an expression of the different surface properties of the clots themselves, caused by the presence of bile in the mixed ones.

Discussion

When minor hemobilia causes symptoms, it is because blood coagulates in the biliary tract and forms solid clots. Between meals, Oddi's sphincter stays closed long enough to allow clotting of even small amounts of blood trapped above it.

A coagulum will often be a cast of the viscus where it is probably formed; it will be branched in the biliary tree (Figs. 5 and 6), cylindrical in the common duct (Fig. 2) and cone-formed in the distal portion (Fig. 9). The shape also probably depends on the patient's position during formation of the clot; with the patient supine, the clots tend to become vermiform (Fig. 12), with the patient upright the clots will form above the sphincter and produce triangular defects on the cholangiogram. This may cause diagnostic difficulties in differentiation between clots, retained calculi (Fig. 11) and contraction of the choledochal sphincter.[24]

These clots rarely acquire clinical significance because they promptly dissolve through the fibrinolytic action of the bile; in this respect, the bile plays the same role as urine and saliva, namely that of clearing their respective ducts from fibrin deposits.[2] The lytic effect may be due either to activation of fibrinolysis in the blood by the bile acids[14] or to the fibrinolytic activity of the bile itself.[9] The high effectiveness of the reaction is evident in case 5B (Fig. 3b) and has also been verified in the experiments which show prompt lysis of blood clots mixed with bile or subjected to bile perfusion.

Our experimental findings *in vivo* correspond to those *in vitro*. Besides some new information on the relation of the clots to the gallbladder mucosa they also confirmed the difference in quality between the solid pure clots and the unstable mixed ones during the first 24 hours. Their further development was related to the bile flow. When the clots were protected in an entirely excluded gallbladder they remained unchanged for at least a week. However, both kinds of clots, whether pure or mixed, diminished or disappeared in four weeks when fully exposed to the bile flow.

In order for clots to cause symptoms of clinical significance, there must clearly be some factor which delays, disturbs, or prevents the normal fibrinolytic properties of bile.

Our experiments show that pure clots, which are prone to develop during minor hemobilia, are more solid than mixed ones—but they also prove that even these more resistant clots dissolve relatively rapidly when exposed to flowing bile.

Instead, the decisive role is played by the bile perfusion—when that fails, the clots remain.

Clinically, such a situation could occur when the bile flow gets either diverted or obstructed. We now have an explanation as to why the clots in symptomatic cases such as ours escaped lysis. They were all caused by minor bleeding and were thus probably solid. But, more importantly, they were protected from the bile flow.

A prolonged diversion of the bile stream through a T-tube was presumably the reason why the clot from a postoperative occult bleeding in Case 3 did not dissolve. Even the gallbladder can serve as a hiding place as in Olsen's[15] case where the clots in the gallbladder had time to turn into calculi.

In other patients the bile flow may be obstructed by the clot itself: in Cases 1 and 6 the clot had stuck above the sphincter, and in Cases 7 and 8 above the confluence of the right and left duct. All four were misinterpreted as gallstones.

When biliary colic is accompanied by obstructive jaundice and no cause is found, it is generally suspected that a small stone has passed. Considering the high frequency of minor hemobilia in gallstone disease

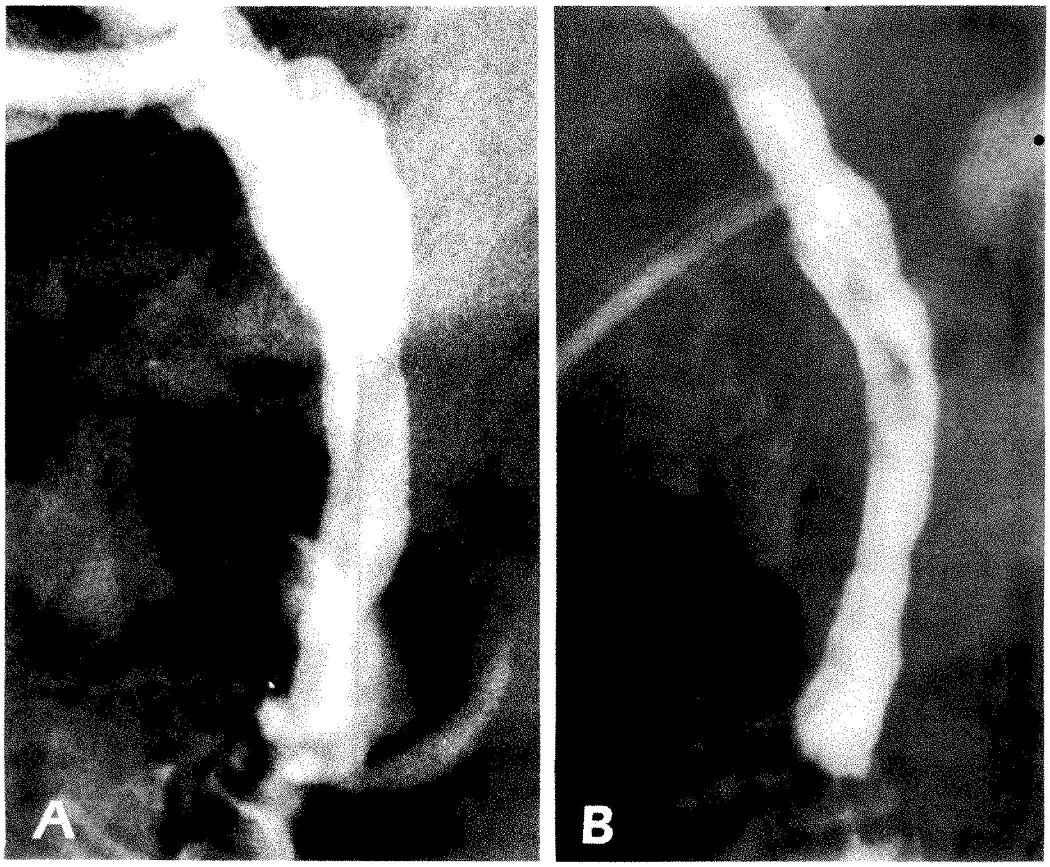


FIG. 12. String- or worm-like clots probably result from minor hemobilia if this occurs while the patient is in the supine position. (A) Nine days after retrieval of a common duct stone from an inflamed common duct containing fibrin morsels, the cholangiogram showed a long cord-like structure, certainly a clot. It disappeared spontaneously. (Surgical Department, CHUV, Lausanne). (B) Eight days after operative removal of a common duct stone there was bleeding through the T-tube and the cholangiogram showed defects, supposedly due to worm-like clots. Perfusion with streptokinase and heparine was started. Renewed cholangiogram a week later showed normal filling. (Ammann, Thurgauisches Kantonspital, Münsterlingen).

and with our present knowledge of clot formation it seems probable that in some cases the obstruction was caused by a clot, as in Case 6, rather than by a passing stone. We recently had a patient who can serve as an example:

A woman suffered two attacks of severe biliary colic; the latter followed by obstructive jaundice. At operation the gallbladder was inflamed and edematous. It contained a large, rugged, solitary stone. The cystic duct was narrow with intact valvulae. There were no stones in the common duct and the passage to the intestine was free. It seems most likely to us that the temporary obstruction in this case was caused by a clot, formed in the common duct.

There is another possible explanation for the appearance of clots in minor hemobilia. If this is persistent, layers of different age will form. Also, the lytic potential of the bile may finally be exhausted. Such a process is evident in Case 4 and could have contributed to the clot formation in Cases 6, 7 and 8. Clots like these, formed from continuous bleeding during an extended period of time, are often particularly firm and solid. One may speculate on the possibility that so-called primary common duct stones, which often are described as "muddy" could have originated in clots from persistent minor hemobilia.

Even clots that promptly lyse may be of clinical significance during their ephemeral existence, not through symptoms but by causing diagnostic errors and being mistaken for calculi as in Cases 2 and 5. We have a suspicion that some of the "retained stones" which have been easily dissolved through perfusion with different solutions have been nothing else than blood clots which in any case would have disappeared through natural fibrinolysis. Look, for example, at the cholangiograms from a case where a suspected stone disappeared within a week after three perfusions with saline and lignocaine.[4] The "retained stone" looks exactly like one of our clots, and not like the round calculi, retrieved from the left hepatic duct (Fig. 11A). The same suspicion is aroused by a cholangiogram (Fig. 11B) published by Schein[24] where a triangular defect, supposedly caused by a stone had disappeared ten days after clamping of the T-tube.

Our research indicates that in biliary obstruction or when defects are found on cholangiography, the possible existence of blood clots in the ducts should be considered even in the absence of overt gastrointestinal hemorrhage. Some clots can be prevented by careful technique and hemostasis during biliary tract operation. In treatment, the surgeon should first try stimulating fibrinolysis by restoring the free flow of bile, or perhaps by perfusing with fibrinolytic agents[12] before resorting to operative removal.

Although nowadays unduly neglected, minor hemobilia is by no means a recent concept. Exactly two centuries ago, Portal[17] warned against misinterpretation and faulty treatment of the syndrome. We agree with him, and we also, for our readers' benefit, accept the good advice in his last sentence:

> It is harder to recognize hemorrhage leaving the liver through the common duct when they are slight in quantity and occur but seldom. The blood then sometimes mixes with the bile or with the gastric juice and is voided in more or less altered form in vomit. Physicians mistake the source of the bleeding when this happens and suspect, sometimes even treat, the patients for lung diseases they do not have. I have seen two hemorrhages of this kind and have established how they were brought about in the most reliable way possible, namely, by autopsy. I shall not go into detail as it would add an undue number of pages to this essay.

> Les hémorragies du foie par le canal cholédoque, ſont bien plus difficiles à connoître que dans les cas précédens; lorſqu'elles ſont très-petites & qu'elles ſurviennent à divers temps, alors le ſang ſe mêle quelquefois avec la bile ou avec le ſuc gaſtrique, & ſort par la bouche plus ou moins altéré. Les Médecins ſe trompent ſur la ſource qui le fournit, ſuppoſent, traitent même des maladies du poumon qui n'exiſtent pas: j'ai l'exemple de deux mépriſes de cette ſorte, dont je me ſuis aſſuré de la manière la plus convaincante, par l'ouverture du corps, j'en ſupprime les détails pour abréger ce Mémoire.

Conclusions

Minor hemobilia is very frequent but rarely of clinical significance. The blood either remains fluid, flowing unobtrusively into the intestine or, if it coagulates, the clot promptly dissolves through the fibrinolytic activity of the bile. Occasionally the clots escape this influence of the bile. They will then remain and act as gall stones for which they may be mistaken.

Acknowledgments

We wish to acknowledge the help of Dr. B. Winistörfer with the histologic data and of Dr. J. W. L. Robinson with the linguistic accuracy. We are indebted to Mrs. W. Boscacci for her untiring secretarial aid.

References

1. Adolph, K.: Gallengangs- and Pankreasdiagnostik. Ferd. Enke Verlag, Stuttgart, 1968, p. 153.
2. Astrup, T.: The Biologic Significance of Fibrinolysis. Lancet, ii:565, 1956.
3. Cahow, C. E., Burrell, M. and Greco, R.: Hemobilia Following Percutaneous Transhepatic Cholangiography. Ann. Surg., 185:235, 1977.
4. Catt, P. B., Hogg, D. F., Clunie, G. J. A., et al.: Retained Biliary Calculi. Ann. Surg., 180:247, 1974.
5. Fisher, E. R. and Creed, D. L.: Clot Formation in the Common Duct. Arch. Surg., 73:261, 1956.
6. Gad, P.: Okkult blødning ved galdesten. Nord. Med., 68:1069, 1962.
7. Hepp, J.: Hemorragies Digestives au Cours des Affections Biliaires. Arch. Mal. Appar. Dig., 48:1589, 1959.
8. Johns, W. A. and Zimmerman, A.: Biliary Obstruction due to Hemobilia Caused by Liver Cell Carcinoma. Ann Surg., 153:706, 1961.
9. King, J. B.: Fibrinolysis by Bile. Thromb. Diath. Haemorrh., 28:299, 1972.
10. van der Linden, W.: Hemobilia: A Case with Recurrent Jaundice Cured by Removal of Blood Clot from the Common Bile Duct. Acta Chir. Scand., 141:455, 1975.
11. Millbourn, E.: Cholangiografiskt påvisade blod koagel i gallvägarna i samband med choledochusingrepp. Nord. Med., 45:103, 1951.
12. Nakayama, F.: Personal communication.
13. Naunyn, B.: Klinik der Cholelithiasis. Leipzig, 1892.
14. Olesen, E. S.: Activation of Fibrinolysis in Guinea-Pig Serum by Bile Acids. Thromb. Diath. Haemorrh., 4:473, 1960.
15. Olsen, W. R.: Personal communication.
16. Plow, E. and Edgington, T. W.: Immunology of Fibrinogen. J. Clin. Invest., 52:273, 1973.
17. Portal, A.: Sur Quelques Maladies du Foie. Hist. de l'Acad. R., 1777:601, 1790.
18. Quast, M. and Clauss, P.: Verschlussikterus durch Hämobile. Zbl. Chir., 96:601, 1971.
19. Räf, L.: Personal communication.
20. Sandblom, P.: Hemobilia. Springfield, Charles C Thomas, 1972.
21. Sandblom, P., Rostan, O., Benz, G. and Saegesser, F.: L'Hémobilie. A Propos de cinq Observations. J. Chir., 109:137, 1975.
22. Sandblom, P., Mirkovitch, V. and Saegesser, F.: Formation and Fate of Fibrin Clots in the Biliary Tract. Ann. Surg., 185:356, 1977.
23. Sandblom, P. and Mirkovitch, V.: Hemobilia: Some Salient Features and their Causes. Surg. Clin. North Am., 57:397, 1977.
24. Schein, C.: Postcholecystectomy Syndromes. New York, Harper and Row, 1978.
25. Svane, S. and Wetteland, P.: Obstructive Blood Thrombus Formation in the Common Bile Duct, Probably Due to a Silk Ligature. Acta Chir. Scand., 144:553, 1978.
26. Wiechel, K. L.: Percutaneous Transhepatic Cholangiography. Acta Chir. Scand. Suppl., 330, p. 35, 1964.

POSTOPERATIVE PAIN

prompt narcotic/analgesic relief without A.P.C.

The principal analgesic ingredient, oxycodone, is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine. The analgesic effect of oxycodone begins within 10 to 15 minutes after oral administration, peaks at 45 minutes, and persists for 3 to 6 hours.† Acetaminophen, a non-narcotic analgesic, complements the pain relief provided by oxycodone.

Summary of Prescribing Information
Contraindications: Hypersensitivity to oxycodone or acetaminophen.

Warnings: *Drug dependence:* Oxycodone can produce drug dependence of the morphine type and may be abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration; prescribe and administer with same caution appropriate to other oral narcotic-containing medications. Subject to the Federal Controlled Substances Act.
Usage in ambulatory patients: Caution patients that oxycodone may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.
Interaction with other Central Nervous System depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) with TYLOX capsules may exhibit additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.
Usage in pregnancy: Safe use not established. Should not be used in pregnant women unless potential benefits outweigh possible hazards.
Usage in children: Should not be administered to children.

Precautions: *Head injury and increased intracranial pressure:* The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.
Acute abdominal conditions: TYLOX capsules or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.
Special risk patients: Administer with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Adverse Reactions: *Most frequent:* Lightheadedness, dizziness, sedation, nausea and vomiting; more prominent in ambulatory than non-ambulatory patients; some of these reactions may be alleviated if the patient lies down. *Others:* euphoria, dysphoria, constipation, skin rash and pruritus.

Dosage and Administration: Dosage should be adjusted according to severity of pain and response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. TYLOX capsules are given orally. Usual adult dose is one capsule every 6 hours as needed for pain.

Drug Interactions: CNS depressant effects may be additive with that of other CNS depressants. See Warnings.
Caution: Federal law prohibits dispensing without prescription.
For information on symptoms/treatment of overdosage, see full prescribing information.
Full directions for use should be read before administering or prescribing.

†Halpern, L.M., and Bonica, J.J., "Analgesics," in Modell, W., ed. Drugs of Choice 1976-1977, St. Louis, The C.V. Mosby Co., 1976, p. 213. 0775

TYLOX® CII

CAPSULES

oxycodone HCl* 4.5 mg,
oxycodone terephthalate* 0.38 mg,
acetaminophen 500 mg

***Warning:** May be habit forming.

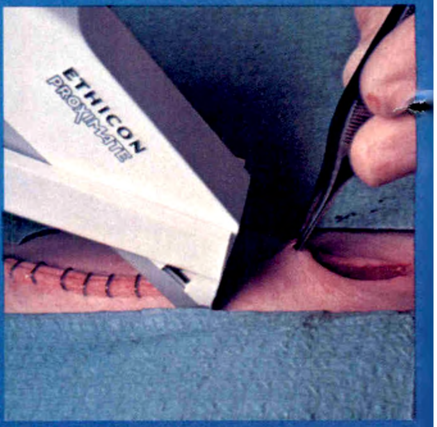
McNEIL

McNeil Laboratories, McNEILAB, Inc., Fort Washington, PA 19034

© McN 1978

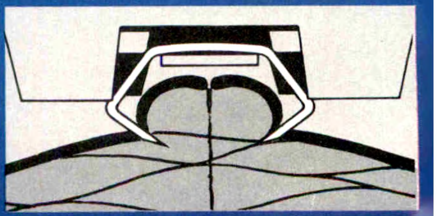
PROXIMATE*
DISPOSABLE SKIN STAPLER

Faster, easier approximation.
Consistent, reliable skin coaptation.



Faster approximation superior cosmetic results

Excellent control, improved accuracy
The PROXIMATE disposable skin stapler is a fast, simple closing device that can reduce operating time and provide excellent cosmetic results. This instrument is designed to fit your hand for comfortable, easy use. Smooth trigger action with less firing force and flexible work angle provide excellent control and accuracy.
Minimal trauma, staples removed easily
The PROXIMATE stapler forms virtually inert rectangular-shaped stainless steel staples. Wound edges are held together by the staple's legs. Tissue reaction and trauma are minimal. Wider crowns keep the staples upright, minimizing rotation, easing removal.
Staple counts and sizes for all closing needs
PROXIMATE products are available with regular and wide staples in counts of 15, 35, and 55 to meet closing needs for short, medium, and long incisions.



Touch skin lightly using centerline indicator to ensure equidistant staple placement across the incision.
Fire, release completely, and withdraw instrument with backward motion.

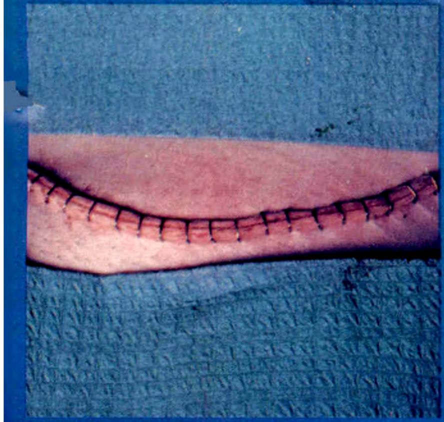
*Trademark ©ETHICON, INC. 1979

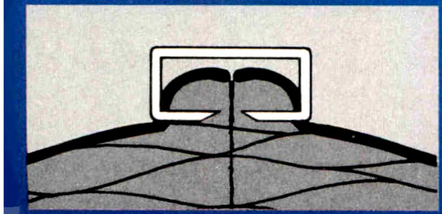
ETHICON

Innovators in wound closure

PROXIMATE staplers have been proven 99% reliable in actual use.**

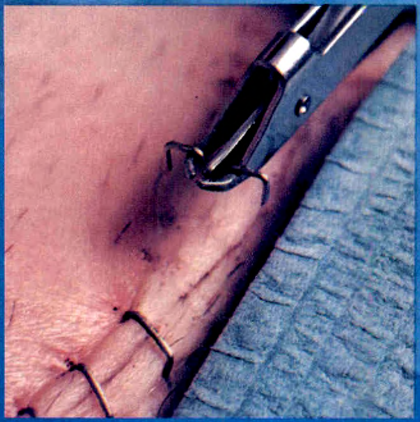
Staples placed accurately.
Designed for precise placement.

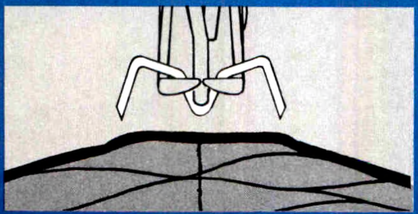




Ample space between staple crown and skin surface minimizes cross-hatching and eases staple extraction. Properly placed staples provide accurate apposition with minimal tension.

Staples removed quickly. Extraction easy for surgeon and patient.





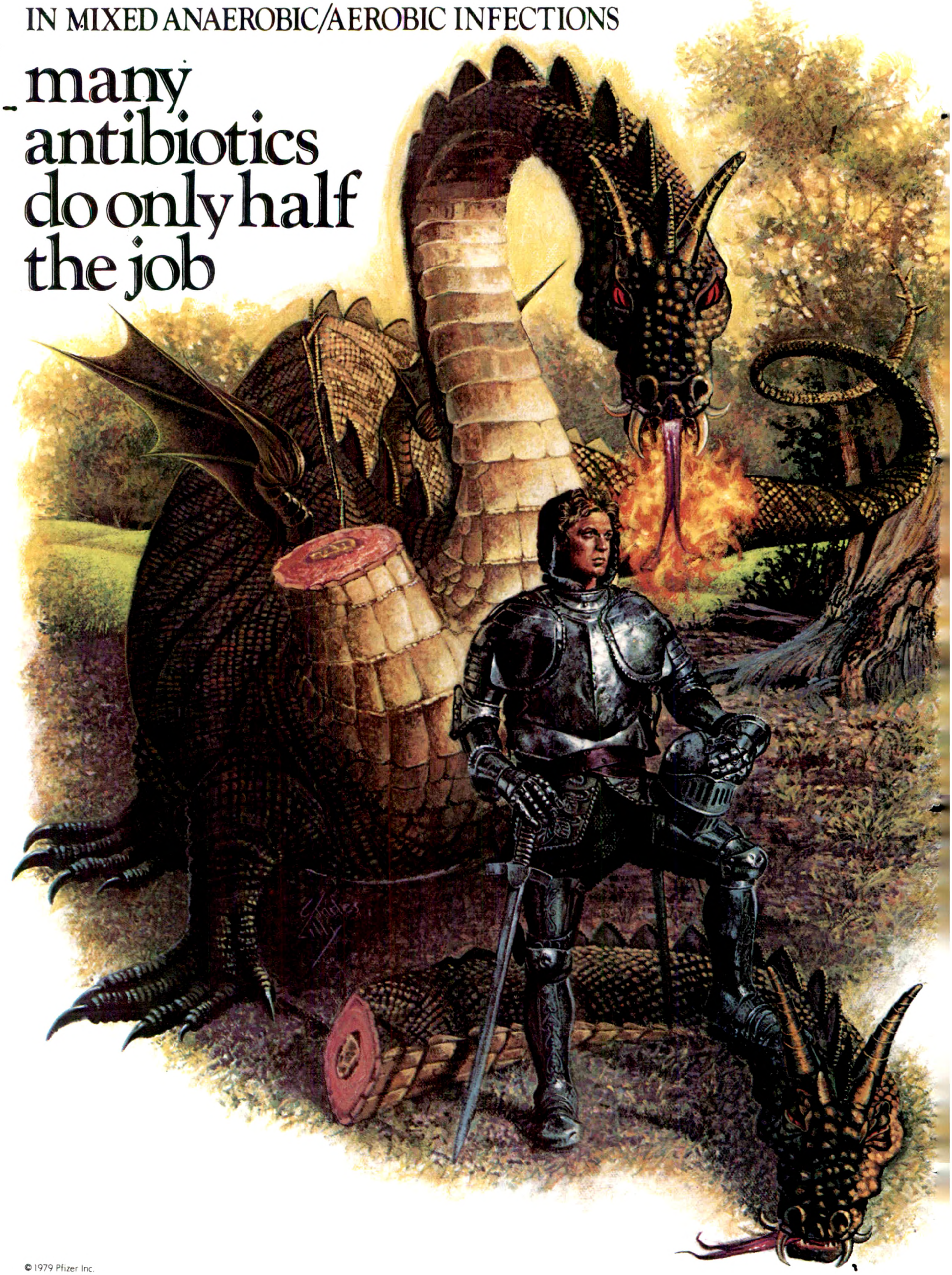
Extractor designed for easy removal of staples. **Simply position jaws beneath staple span, squeeze handles until fully closed, and lift staple.**

Superior cosmetic results.

**Based on data on file at ETHICON, INC.
for PSR35 and PSW35.

IN MIXED ANAEROBIC/AEROBIC INFECTIONS

many antibiotics do only half the job



© 1979 Pfizer Inc.

combat both anaerobes* and gram-negative aerobes* with one antibiotic

GEOPEN® IM/IV

(CARBENICILLIN DISODIUM)

1-gm, 2-gm, 5-gm, and 10-gm vials and 30-gm Bulk Pharmacy Package

Indications: Primarily for treatment of infections due to susceptible strains of *Pseudomonas aeruginosa, Proteus* species (particularly indole-positive strains), and certain *Escherichia coli.*
Clinical effectiveness has been demonstrated in the following infections when due to these organisms: Severe systemic infections and septicemia, including meningitis due to *Hemophilus influenzae* and *Streptococcus pneumoniae*; genitourinary tract infections including those due to *Neisseria gonorrhoeae, Enterobacter,* and *S. faecalis* (enterococcus); acute and chronic respiratory infections (though clinical improvement has been shown, bacteriologic cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis); soft-tissue infections. Also indicated in the following infections due to susceptible anaerobic bacteria: Septicemia; lower respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, pelvic inflammatory disease, pelvic abscess and salpingitis; skin and soft-tissue infections.
Although indicated primarily in gram-negative infections, activity against gram-positive organisms should be kept in mind when both gram-positive and gram-negative organisms are isolated (see **Actions**).
In infections due to certain susceptible strains of *Ps. aeruginosa,* clinical efficacy may be enhanced by combined therapy with gentamicin sulfate in full therapeutic dosages (see gentamicin sulfate package insert).
NOTE: During therapy sensitivity testing should be repeated frequently to detect the possible emergence of resistant organisms.
Actions: Organisms found to be susceptible *in vitro* include: GRAM-NEGATIVE ORGANISMS—*Ps. aeruginosa, Proteus mirabilis, Pr. morgani, Pr. rettgeri, Pr. vulgaris, E. coli, Enterobacter* spp, *Salmonella* spp, *H. influenzae, Neisseria* spp, *Bacteroides* spp, and *Fusobacterium* spp. GRAM-POSITIVE ORGANISMS—*Staphylococcus aureus* (non-penicillinase producing), *Staph. albus, S. pneumoniae,* beta-hemolytic streptococci, *S. faecalis, Clostridium* spp, *Peptococcus* spp, and *Peptostreptococcus* spp.
In vitro synergism between Geopen (carbenicillin disodium) and gentamicin sulfate has been demonstrated for certain strains of *Ps. aeruginosa.* Some newly emerging pathogenic strains of *Herellea, Mima, Citrobacter,* and *Serratia* have also shown *in vitro* susceptibility.
Not stable in the presence of penicillinase. Most *Klebsiella* species are resistant. Some strains of *Pseudomonas* have developed resistance fairly rapidly.
Contraindications: Known penicillin allergy.
Warnings: Serious and occasional fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.
Observe patients with renal impairment for bleeding manifestations and adhere strictly to dosage recommendations; if bleeding manifestations appear, discontinue antibiotic and institute appropriate therapy.
Individuals with history of penicillin hypersensitivity reactions have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, appropriate therapy should be instituted and discontinuance of carbenicillin therapy considered, unless the infection is life threatening and only amenable to carbenicillin therapy. The usual agents (antihistamines, pressor amines, and corticosteroids) should be readily available.
SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.
Usage in Pregnancy: Safety for use in pregnancy has not been established.
Precautions: As with any other potent agent, it is advisable to check periodically for organ-system dysfunction, including renal, hepatic, and hematopoietic systems, during prolonged therapy. Emergence of resistant organisms, such as *Klebsiella* spp and *Serratia* spp, which may cause superinfection, should be kept in mind. Each gram contains 4.7 mEq sodium; in patients where sodium restriction is necessary, such as cardiac patients, periodic electrolyte determinations and monitoring of cardiac status should be made. In a few patients receiving high doses, hypokalemia has been reported; periodic serum potassium determinations should be made and corrective measures should be implemented when necessary. As with any penicillin preparation, an allergic response, including anaphylaxis, may occur, particularly in a hypersensitive individual. Cases of gonorrhea with a suspected primary lesion of syphilis should have darkfield examinations before treatment. In all other cases where concomitant syphilis is suspected, monthly serological tests should be made for a minimum of 4 months.
Intramuscular injections should be made well within the body of a relatively large muscle (not into the lower and mid-third of the upper arm), and aspiration is necessary to help avoid inadvertent injection into a blood vessel. Intravenous infusion should be given as slowly as possible. Reconstituted solution should be discarded after 24 hours if stored at room temperature, after 72 hours if refrigerated. **Reconstituted Bulk Pharmacy Package solution should not be used for direct infusion.** The maximum recommended dose is 40 gm per day; intramuscular injections should not exceed 2 gm per injection.
Adverse Reactions: *Hypersensitivity Reactions*— Skin rashes, pruritus, urticaria, drug fever, and anaphylactic reactions. *Gastrointestinal Disturbances*— Nausea. *Hemic and Lymphatic Systems*— Anemia, thrombocytopenia, leukopenia, neutropenia, and eosinophilia. *Blood, Hepatic, and Renal Studies*— SGOT and SGPT elevations have been observed, particularly in children. To date, no clinical manifestations of hepatic or renal disorders have been demonstrated. *CNS*— Convulsions or neuromuscular irritability could occur with excessively high serum levels. *Other*— Pain at the site of injection, rarely accompanied by induration; in uremic patients receiving high doses (24 gm/day), hemorrhagic manifestations associated with abnormalities of coagulation tests, such as clotting and prothrombin time. *Vein Irritation and Phlebitis*— Particularly when undiluted solution is injected directly into the vein.
How Supplied: Available in 1-gm, 2-gm, and 5-gm vials for IM/IV use; 2-gm, 5-gm, and 10-gm Piggyback Units for IV use; and 30-gm Bulk Pharmacy Package.
For Full Prescribing Information, please see package insert.

ROERIG Pfizer

A division of Pfizer Pharmaceuticals, New York, New York 10017

***susceptible strains of indicated organisms at indicated sites**

What cancer can't kill:

HOPE. LOVE. COMPASSION. DIGNITY. TENDERNESS. UNDERSTANDING.

Because now there's a book of sound advice for everyone whose loved one has cancer.

How do you cope with cancer when someone you care for is the victim? How can you deal with the anger, fear and anxiety? Until now, the answer was a vague one. Today, however, there is a book—by an expert—that is a straightforward, wise, human discussion that can truly help you. It avoids both extreme anxiety and passive acceptance, looking for a middle way of reacting that may actually improve the chances of a cure.

Doing for yourself—with the help of an expert.

Out of the experience of thousands of patients, Dr. Cantor talks about every emotional consequence of the cancer experience. He discusses such vital emotional issues as faith in the physician; fear of abandonment; the process of restitution; the failure of treatment; how different types of marriages and family relationships are likely to respond; handling depression, and much more. Just about everything you could ever want to know, every piece of advice you could ever need, is contained in *And A Time to Live.*

If you need help getting through your experience with cancer in someone you love, you need this book. It will help you have the kind of hope you never thought possible.

"A fine and useful book, unusual in its scope, insight, and compassion."
—ALLEN B. WHEELIS, MD., author of *The Seeker*

"An extraordinarily fine book . . . It is full of vitally important information and wise counsel for people who have cancer and for all who relate to them as professionals, family members, or friends."
—NEVITT SANFORD, author of *The Authoritarian Personality*

AND A TIME TO LIVE
Toward Emotional Well-Being During the Crisis of Cancer
by Dr. Robert Chernin Cantor
$9.95

At your bookstore, or:

HARPER & ROW, Publishers
Attn: R. Brengel
10 East 53rd Street
New York, N.Y. 10022

Please send me ________ copies of *And A Time to Live* @ $9.95 per copy plus 75¢ for postage and handling. If not satisfied, I may return the book(s) within 10 days for a full refund. I enclose ☐ check ☐ money order in the amount of $________ total. (Please add applicable sales tax.)

Name ____________________
Address ____________________
City ____________ State ______ Zip ______

M.V.I.® (Multi-Vitamin Infusion)

Each 10 cc. ampul† or 5 cc. Concentrate vial†† provides:

Ascorbic acid (C)	500 mg.
Vitamin A*	10,000 I.U.
Vitamin D* (ergocalciferol)	1,000 I.U.
Thiamine HCl (B_1)	50 mg.
Riboflavin (B_2)**	10 mg.
Pyridoxine HCl (B_6)	15 mg.
Niacinamide	100 mg.
Dexpanthenol	25 mg.
Vitamin E* (dl-alpha tocopheryl acetate)	5 I.U.

†With sorethytan laurate 1%, sodium hydroxide 1%, butylated hydroxytoluene 0.003%, butylated hydroxyanisole 0.0008%; and gentisic acid ethanolamide 2% as preservative.

††With propylene glycol 30% and gentisic acid ethanolamide 2% as stabilizers and preservatives, sodium hydroxide for pH adjustment, sorethytan laurate 1.6%, butylated hydroxytoluene 0.006%, butylated hydroxyanisole 0.0015%.

*Oil-soluble vitamins A, D and E water solubilized with sorethytan laurate.

**In Concentrate as riboflavin-5-phosphate.

BRIEF SUMMARY

INDICATIONS: *in emergency feedings*– Surgery, extensive burns, fractures and other trauma, severe infectious diseases, comatose states, etc. may provoke a "stress" situation with profound alterations in the body's metabolic demands and consequent tissue depletion of nutrients. As a result, wound healing may be impaired, enzyme activity disturbed, hematopoietic tissues affected; hypoproteinemia and edema may appear; convalescence is thus prolonged.

In such patients M.V.I. (administered in intravenous fluids under proper dilution) contributes optimum vitamin intake toward maintaining the body's normal resistance and repair processes.

DIRECTIONS FOR USE: M.V.I. is ready for immediate use when added to intravenous infusion fluids.

For intravenous feeding, one daily dose of 10 cc. of M.V.I. or 5 cc. of M.V.I. Concentrate added directly to not less than 500 cc., preferably 1,000 cc., of intravenous dextrose, saline or similar infusion solutions…plasma, protein hydrolysates, etc.

PRECAUTION: Allergic reaction has been known to occur following intravenous administration of solutions containing thiamine.

CAUTION: Not to be given as a direct undiluted intravenous injection as it may give rise to dizziness, faintness, etc.

THERAPEUTIC NOTE: Intravenous use should be discontinued as early as practical in favor of an intramuscular or oral vitamin preparation, if deemed advisable.

HOW SUPPLIED: M.V.I.–10 cc. ampuls, boxes of 25 and 100 (NSN 6505-00-455-9955/NSN 6505-00-424-9808A).

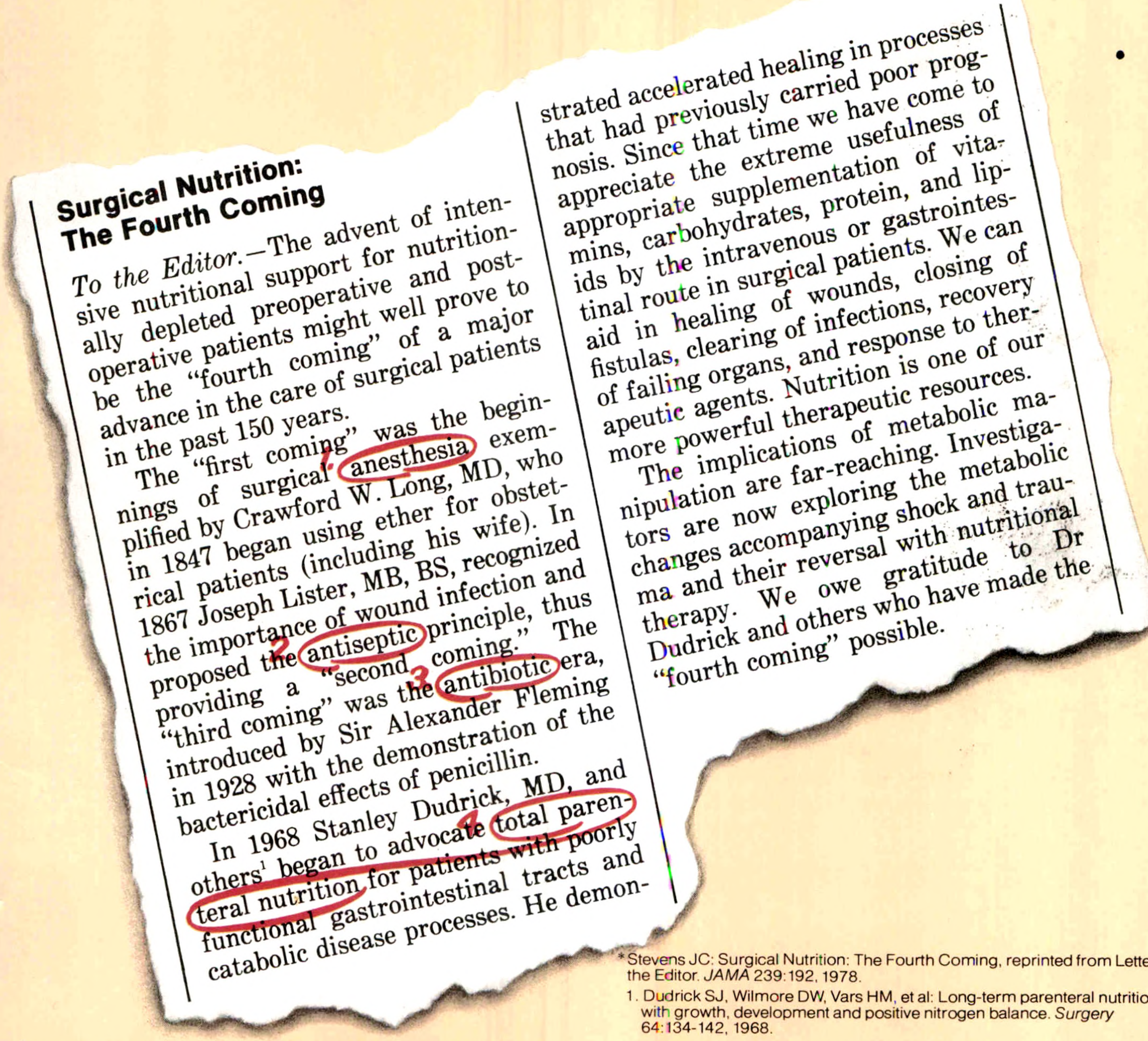
M.V.I. CONCENTRATE–5 cc. vials, boxes of 25. Available in 100s only (NSN 6505-00-212-6156A).

USV LABORATORIES

USV Laboratories, Division
USV Pharmaceutical Corp.
Tuckahoe, New York 10707

Four Discoveries That Changed Medical History

Reprinted from Letters to the Editor, JAMA.*



Surgical Nutrition: The Fourth Coming

To the Editor.—The advent of intensive nutritional support for nutritionally depleted preoperative and postoperative patients might well prove to be the "fourth coming" of a major advance in the care of surgical patients in the past 150 years.

The "first coming" was the beginnings of surgical 1. anesthesia exemplified by Crawford W. Long, MD, who in 1847 began using ether for obstetrical patients (including his wife). In 1867 Joseph Lister, MB, BS, recognized the importance of wound infection and proposed the 2 antiseptic principle, thus providing a "second coming." The "third coming" was the 3 antibiotic era, introduced by Sir Alexander Fleming in 1928 with the demonstration of the bactericidal effects of penicillin.

In 1968 Stanley Dudrick, MD, and others[1] began to advocate 4 total parenteral nutrition for patients with poorly functional gastrointestinal tracts and catabolic disease processes. He demonstrated accelerated healing in processes that had previously carried poor prognosis. Since that time we have come to appreciate the extreme usefulness of appropriate supplementation of vitamins, carbohydrates, protein, and lipids by the intravenous or gastrointestinal route in surgical patients. We can aid in healing of wounds, closing of fistulas, clearing of infections, recovery of failing organs, and response to therapeutic agents. Nutrition is one of our more powerful therapeutic resources.

The implications of metabolic manipulation are far-reaching. Investigators are now exploring the metabolic changes accompanying shock and trauma and their reversal with nutritional therapy. We owe gratitude to Dr Dudrick and others who have made the "fourth coming" possible.

---

*Stevens JC: Surgical Nutrition: The Fourth Coming, reprinted from Letters to the Editor. *JAMA* 239:192, 1978.

1. Dudrick SJ, Wilmore DW, Vars HM, et al: Long-term parenteral nutrition with growth, development and positive nitrogen balance. *Surgery* 64:134-142, 1968.

We have reprinted the above letter to the editor of JAMA because we believe it should be seen by every physician concerned with the nutritional status of hospitalized patients. The letter writer ranks hyperalimentation with some of the monumental medical discoveries of the past—anesthesia, antisepsis and antibiotics. Few who have witnessed the lifesaving benefits of this technique would argue the point.

We at USV are proud of our continuing role in hyperalimentation through the development and refinement of the comprehensive multivitamin infusion M.V.I.®, as well as sponsorship of research and educational programs in parenteral nutrition.

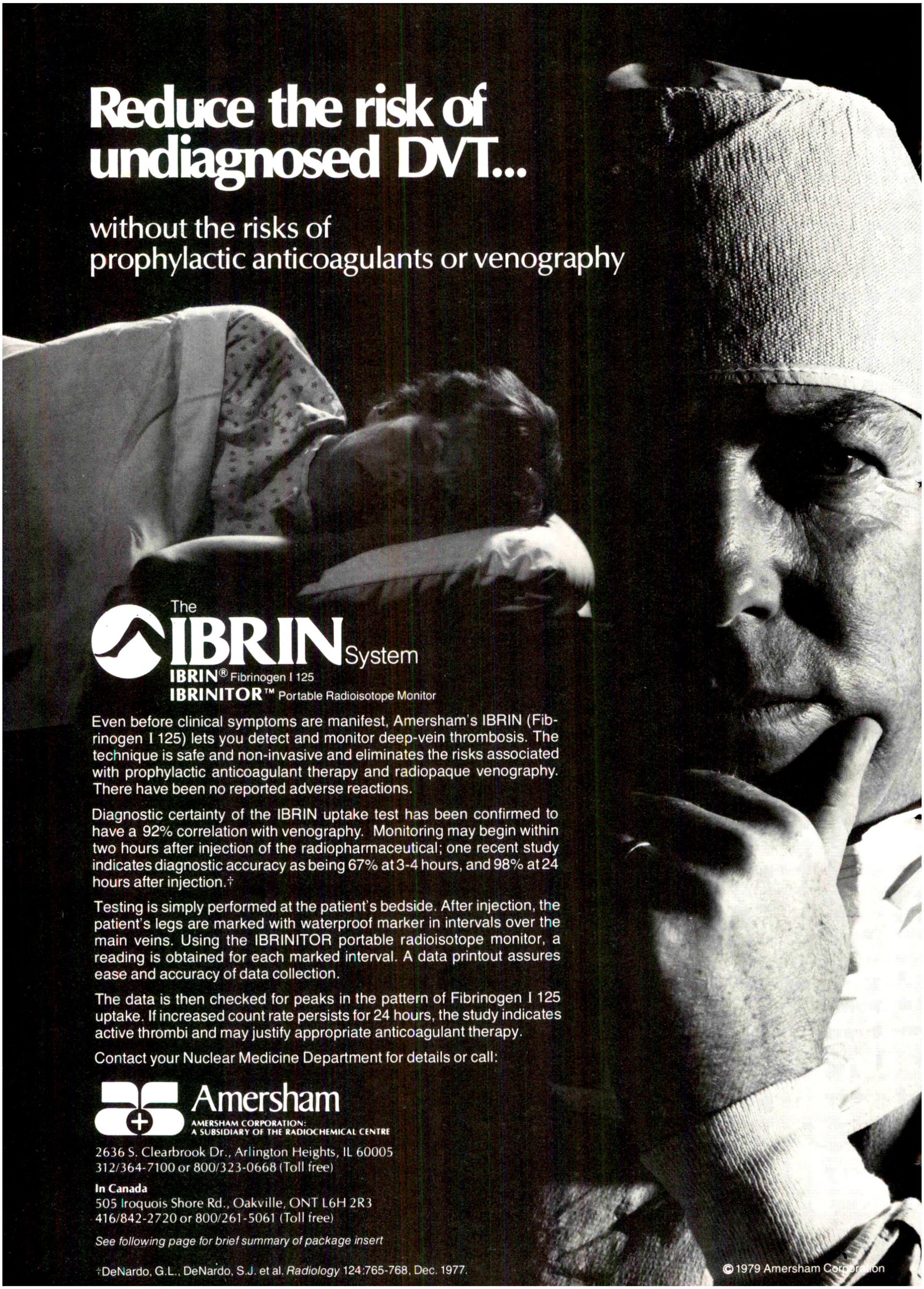
To learn how hyperalimentation may reduce morbidity and mortality in a wide variety of clinical situations, just write us on your letterhead requesting a comprehensive monograph, tape-cassette program and/or film on the subject.

USV LABORATORIES

USV Laboratories, Division
USV Pharmaceutical Corp.
Tuckahoe, New York 10707

HYPERALIMENTATION

M.V.I.® (MULTI-VITAMI INFUSION)



Reduce the risk of undiagnosed DVT...

without the risks of prophylactic anticoagulants or venography

The **IBRIN** System

IBRIN® Fibrinogen I 125
IBRINITOR™ Portable Radioisotope Monitor

Even before clinical symptoms are manifest, Amersham's IBRIN (Fibrinogen I 125) lets you detect and monitor deep-vein thrombosis. The technique is safe and non-invasive and eliminates the risks associated with prophylactic anticoagulant therapy and radiopaque venography. There have been no reported adverse reactions.

Diagnostic certainty of the IBRIN uptake test has been confirmed to have a 92% correlation with venography. Monitoring may begin within two hours after injection of the radiopharmaceutical; one recent study indicates diagnostic accuracy as being 67% at 3-4 hours, and 98% at 24 hours after injection.†

Testing is simply performed at the patient's bedside. After injection, the patient's legs are marked with waterproof marker in intervals over the main veins. Using the IBRINITOR portable radioisotope monitor, a reading is obtained for each marked interval. A data printout assures ease and accuracy of data collection.

The data is then checked for peaks in the pattern of Fibrinogen I 125 uptake. If increased count rate persists for 24 hours, the study indicates active thrombi and may justify appropriate anticoagulant therapy.

Contact your Nuclear Medicine Department for details or call:

Amersham
AMERSHAM CORPORATION:
A SUBSIDIARY OF THE RADIOCHEMICAL CENTRE

2636 S. Clearbrook Dr., Arlington Heights, IL 60005
312/364-7100 or 800/323-0668 (Toll free)

In Canada
505 Iroquois Shore Rd., Oakville, ONT L6H 2R3
416/842-2720 or 800/261-5061 (Toll free)

See following page for brief summary of package insert

---

†DeNardo, G.L., DeNardo, S.J. et al. *Radiology* 124:765-768, Dec. 1977.

© 1979 Amersham Corporation

The
IBRIN System

IBRIN® Fibrinogen I 125
IBRINITOR™ Portable Radioisotope Monitor

INDICATIONS
IBRIN is indicated for use in prospective studies for the early detection and subsequent monitoring of developing deep-vein thrombosis and in diagnostic studies for the detection of established thrombosis in the legs.

A. The IBRIN (Fibrinogen I 125) test is indicated in patients with signs and /or symptoms suggestive of deep-vein thrombosis with or without associated pulmonary embolism or in patients with pulmonary embolism, with or without evidence of peripheral deep-vein thrombosis. In patients with established, old or "inactive" thrombi, the test will be positive only if radionuclide-labeled fibrin deposition occurs in a sufficient quantity to allow detection. Its use is not contraindicated in patients on anticoagulants.

B. The IBRIN (Fibrinogen I 125) test is indicated for the detection of thrombus formation in patients undergoing major orthopedic or other surgical procedures, myocardial infarction, pulmonary disease, malignant disease and other medical conditions known to predispose to thromboembolism.

CONTRAINDICATIONS
There are no known contraindications to the use of IBRIN. However, it should be noted that the iodides given to block the uptake of ^{125}I by the thyroid gland are contraindicated in patients with a known sensitivity to the iodides.

WARNINGS
This radiopharmaceutical should not be administered to patients under 18 years of age, to patients who are pregnant, or to patients who are lactating, unless the information to be gained outweighs the potential risk.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of child bearing capability should be performed during the first few (approximately 10) days following the onset of menses. Nursing mothers should substitute formula feeding after the administration of Fibrinogen I 125.

Extraordinary precautions have been taken in the preparation of IBRIN (Fibrinogen I 125) to eliminate the possible transmission of hepatitis. Nevertheless, the remote risk of hepatitis associated with the administration of Fibrinogen I 125 cannot be entirely eliminated. The finding of viral hepatitis in any patient up to six months after the administration of IBRIN should be reported to Amersham for further evaluation, since there are numerous possible sources of hepatitis infection.

PRECAUTIONS
Care should be taken to insure minimum radiation exposure to the patient, consistent with proper patient management, and to insure minimum radiation exposure to occupational workers.

This drug contains radioactive materials which must be handled only by qualified personnel in conformity with Nuclear Regulatory Commission, agreement state, or other appropriate government regulations. Care must be taken to avoid excessive exposure to its radiation. Shielding or equivalent radiation protective measures must be used.

This product is prepared from units of human plasma which have been tested using RIA methods and found non-reactive for Hepatitis B surface antigen. Approved detection methods are not sensitive enough to detect all infectious units of blood or all possible cases of hepatitis. However, IBRIN has been prepared from single donor plasma and has been injected into recipients without incidence of fibrinogen related Hepatitis B as evidenced by periodic physical examination and laboratory testing (liver profile, CBC, and Hepatitis B surface antigen and antibody by radioimmunoassay) of the recipients.

There are a number of clinical circumstances requiring consideration in the interpretation of the test results. (See complete Package Insert.)

Fibrinogen I 125 scanning should preferably be performed prior to venography if both procedures are contemplated, since venography may cause increases in count rate making interpretation of post-venography monitoring data difficult.

Adequate reproduction studies on animals have not been performed to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. Fibrinogen I 125 should be used in pregnant women only when clearly needed.

ADVERSE REACTIONS
There has been no reported incidence of allergic or anaphylactic reactions following the intravenous administration of IBRIN.

Amersham
AMERSHAM CORPORATION:
A SUBSIDIARY OF THE RADIOCHEMICAL CENTRE

2636 S. Clearbrook Dr., Arlington Heights, IL 60005
312/364-7100 or 800/323-0668 (Toll free)

In Canada
505 Iroquois Shore Rd., Oakville, ONT L6H 2R3
416/842-2720 or 800/261-5061 (Toll free)

New!

SURGICAL ENDOCRINOLOGY
Clinical Syndromes

●

Edited by
STANLEY R. FRIESEN, M.D., Ph.D.(Surg.)
with 28 contributors

Here is up-to-the-minute, useable information on the known endocrine syndromes requiring the attention of surgeons and other physicians. The book encompasses all the surgically significant endocrinopathies, both common and rare, all ages of patients, from the newborn to the elderly, and all accepted techniques of clinical and laboratory diagnosis, as well as surgical and conservative management.

The relevant basic sciences are integrated with current diagnostic and therapeutic techniques. Each of the contributors is a leading authority writing on his own area of special interest.

Among the unique features of this text you'll find an illuminating commentary on each chapter by Dr. Friesen . . . step-by-step diagnostic flowcharts . . . a central table of the humoral and biological actions of 20 important endocrine syndromes . . . mnemonic names for the syndromes . . . diagrammatic illustrations depicting the pathophysiology of each syndrome as a composite of clinical findings.

The volume presents a wealth of extraordinarily current developments, featuring information on such innovative concepts and practices as the APUD series of endocrine cells—their origin, identification, and clinical applications, and the future surgical management of endocrinopathies via transposition and transplantation of endocrine tissues.

430 Pages / 110 Illustrations / 1978 / $29.00

Lippincott

J. B. LIPPINCOTT COMPANY
East Washington Square ● Phila., Pa. 19105

In Canada: J. B. Lippincott Company of Canada Ltd.
75 Horner Avenue, Toronto, Ontario M8Z 4X7

Please send me:
Friesen: SURGICAL ENDOCRINOLOGY $29.00
Name ______________________
Address ______________________
City ______________ State ______ Zip ______

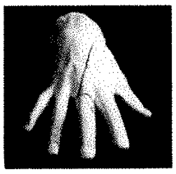
☐ Payment enclosed (Save postage and handling)
☐ Charge and bill me (Plus postage and handling)

Also available at your medical bookstore 8/79

See below for important product information concerning warnings, adverse reactions, patient selection and prescribing and precautionary recommendations.

Let the healing begin
in pain-free comfort

Marcaine® hydrochloride
brand of
# bupivacaine hydrochloride
with or without epinephrine 1:200,000



Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

Allergic reactions, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

References:

1. Moore DC, Bridenbaugh LD, Thompson GE: Bupivacaine hydrochloride: a summary of investigational use in 3,274 cases. *Anesth Analg* 50: 856-872, 1971.
2. Moore DC, Bridenbaugh LD, Thompson GE, et al: Bupivacaine: a review of 11,080 cases. *Anesth Analg* 57:42-53, 1978.

BREON
BREON LABORATORIES, INC.
90 Park Avenue, New York, N.Y. 10016

FORMULA

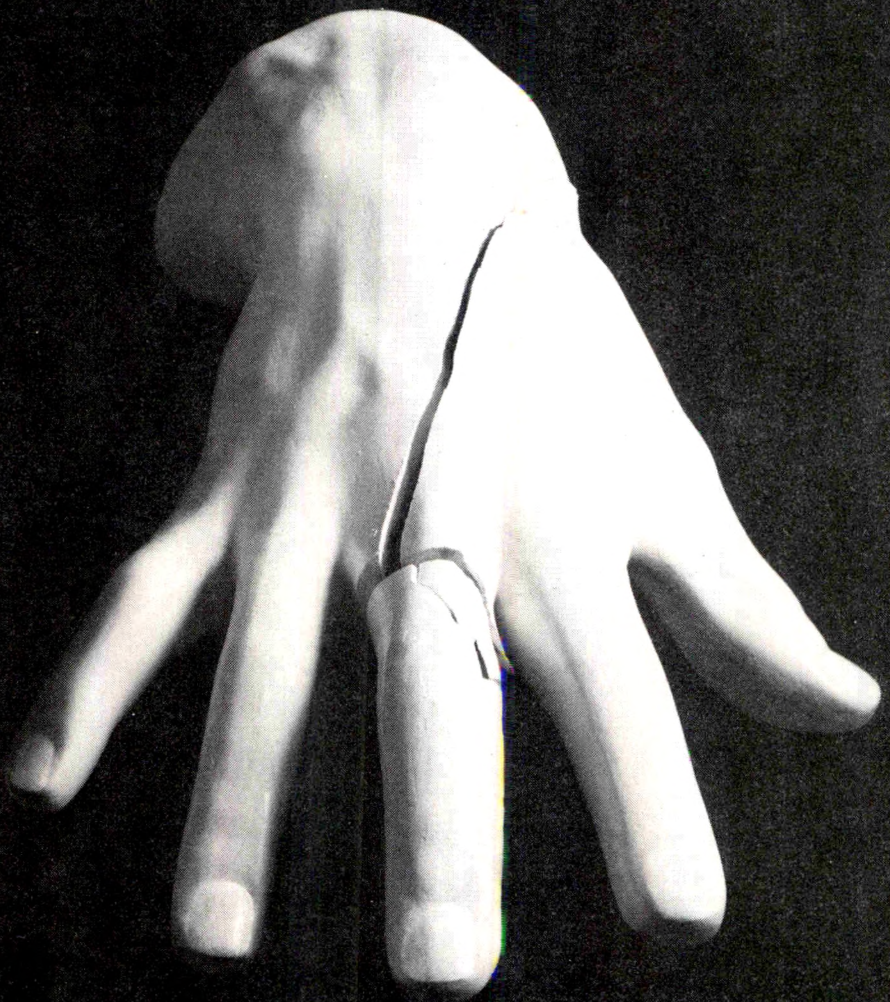
PRODUCT IDENTIFICATION			MULTIPLE DOSE VIAL						SINGLE DOSE AMPUL				
Marcaine HCl (brand of bupivacaine HCl) %	mg./ml.	Epinephrine* (as bitartrate) Dilution	Methylparaben mg./ml.	Sodium Bisulfite mg./ml.	Thioglycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.	Sodium Bisulfite mg./ml.	Thioglycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.
0.25	2.5	—	1	—	—	—	—	—	—	—	—	—	—
0.25	2.5	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.5	5.0	—	1	—	—	—	—	—	—	—	—	—	—
0.5	5.0	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.75	7.5	—							—	—	—	—	—
0.75	7.5	1:200,000	Not Available in Vials						.5	.001	2	.0017	0.1

Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved.

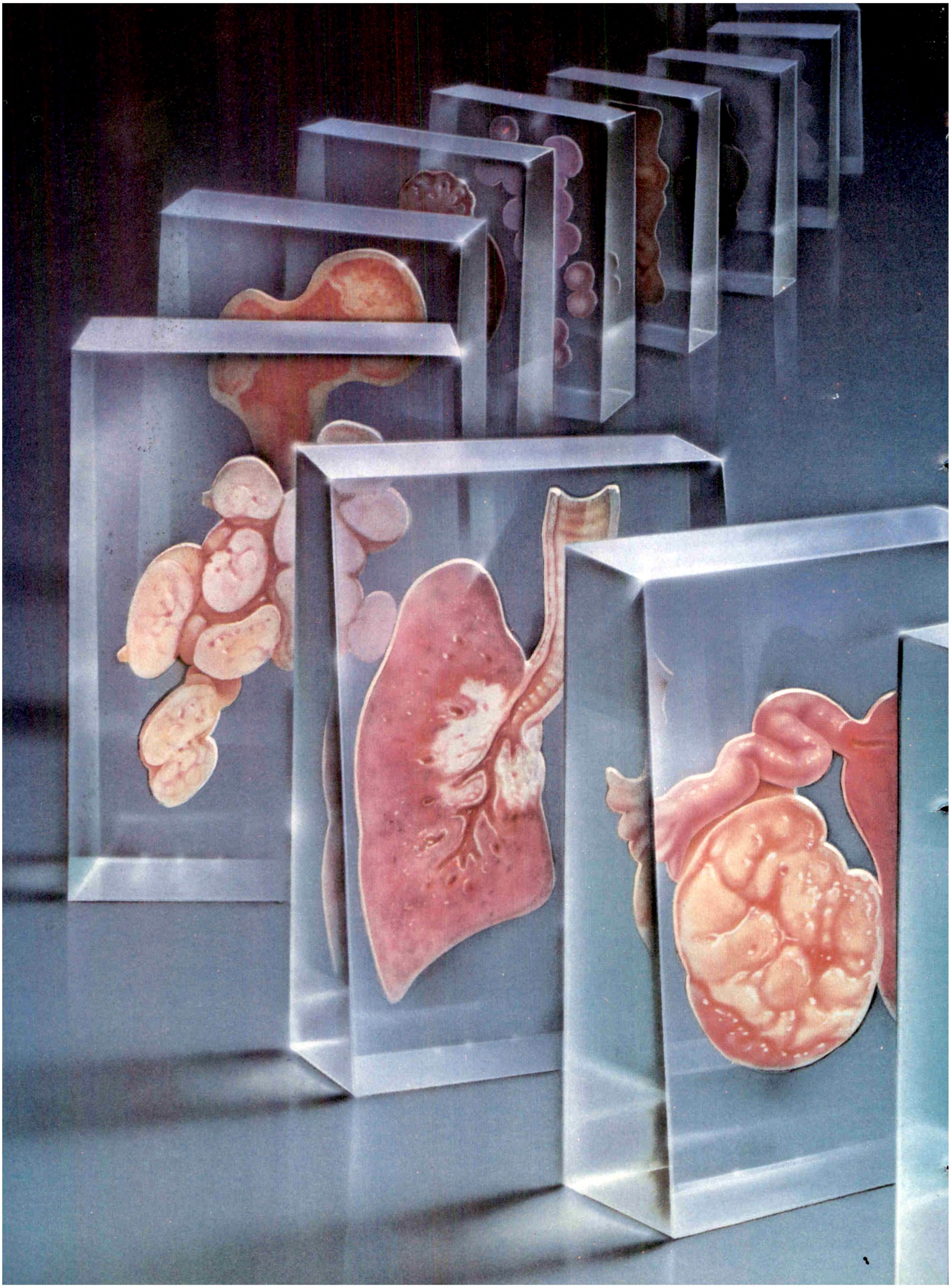
Federal law prohibits dispensing without a prescription.

Let the healing begin in pain-free comfort



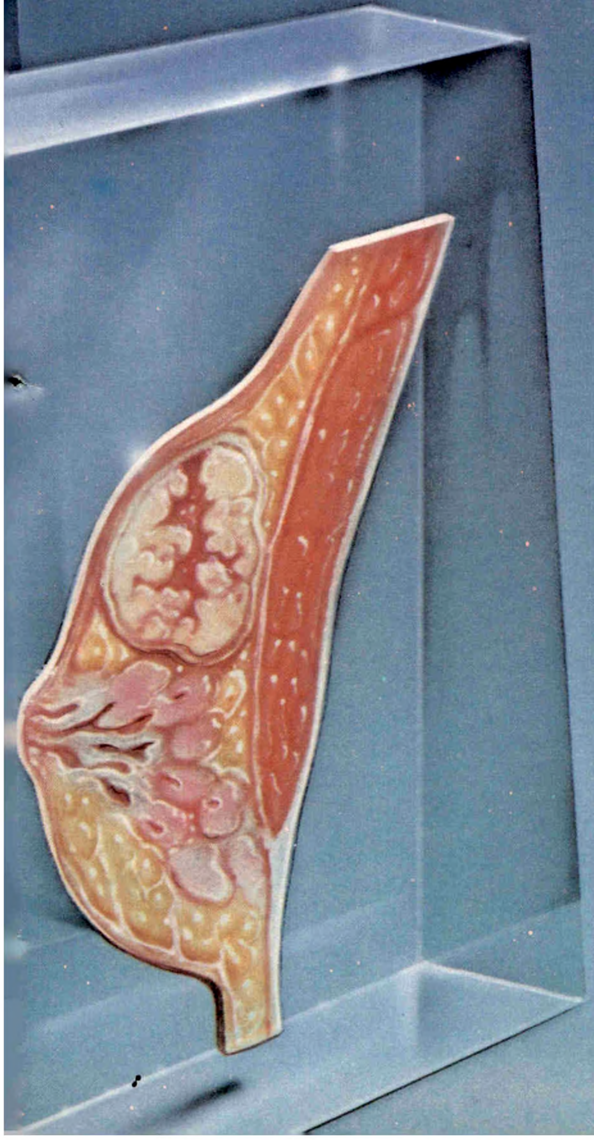
Of all commonly used local anesthetics,
Marcaine® defers pain for so long,
there's significantly less need
for postoperative analgesics.[1,2]

Marcaine® hydrochloride
brand of
bupivacaine hydrochloride
with or without epinephrine 1:200,000
See adjacent page for prescribing information.



Over 20 years of progress in cancer chemotherapy

CYTOXAN®
(CYCLOPHOSPHAMIDE)



a chemotherapeutic agent of ever increasing importance

Since its introduction in 1959 as one of the first potent cytotoxic agents, intensive pharmacological and clinical studies with CYTOXAN have led to broad usefulness in 15 malignancies, with predictable response.

Further, refinements in the careful usage of CYTOXAN have resulted in increased response rates in several neoplasms. For instance, with intermittent dosage schedules of 10 mg/kg/week instead of daily schedules, the response rate in rhabdomyosarcoma increases to over 80%, to about 65% in neuroblastoma, and to about 60% in Ewing sarcoma.[1]

injectable and oral dosage forms

CYTOXAN is available in vials of 100 mg, 200 mg, and 500 mg for injection and in oral tablets of 25 mg and 50 mg.

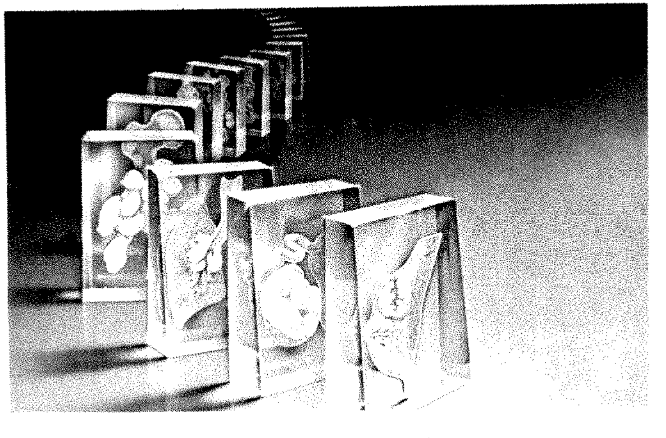
Chemotherapy with CYTOXAN, as with other drugs used in cancer chemotherapy, is potentially hazardous and fatal complications can occur. It is recommended that it be administered only by physicians aware of the associated risks.

1. Block JB: Drugs for cancer, in Modell W, (ed): *Drugs of Choice 1978-1979.* St Louis, C. V. Mosby Co, 1978, pp 580-608.

Mead Johnson
PHARMACEUTICAL DIVISION

CYTOXAN®
(CYCLOPHOSPHAMIDE)
adaptable broad spectrum cancer chemotherapy

For prescribing information, please see the following page.



CYTOXAN®
(CYCLOPHOSPHAMIDE)

INDICATIONS

A. Frequently responsive myeloproliferative and lymphoproliferative disorders:
  1. Malignant lymphomas (Stages III and IV, Peter's Staging System).
    a. Hodgkin's disease.
    b. Follicular lymphoma.
    c. Lymphocytic lymphosarcoma.
    d. Reticulum cell sarcoma.
    e. Lymphoblastic lymphosarcoma.
    f. Burkitt's lymphoma.
  2. Multiple myeloma.
  3. Leukemias:
    a. Chronic lymphocytic leukemia.
    b. Chronic granulocytic leukemia (it is ineffective in acute blastic crises).
    c. Acute myelogenous and monocytic leukemia.
    d. Acute lymphoblastic (stem-cell) leukemia in children (cyclophosphamide given during remission is effective in prolonging its duration).
  4. Mycosis fungoides (advanced disease).

B. Frequently responsive solid malignancies.
  1. Neuroblastoma (in patients with disseminated disease).
  2. Adenocarcinoma of the ovary.
  3. Retinoblastoma.

C. Infrequently responsive malignancies:
  1. Carcinoma of the breast.
  2. Malignant neoplasms of the lung.

WARNINGS

Since Cytoxan has been reported to be more toxic in adrenalectomized dogs, adjustment of the doses of both replacement steroids and Cytoxan may be necessary for the adrenalectomized patient.

The rate of metabolism and the leukopenic activity of Cytoxan reportedly are increased by chronic administration of high doses of phenobarbital. The physician should be alert for possible combined drug actions, desirable or undesirable, involving Cytoxan even though Cytoxan has been used successfully concurrently with other drugs, including other cytotoxic drugs.

Cytoxan may interfere with normal wound healing.

Usage in Pregnancy. Cytoxan can be teratogenic or cause fetal resorption in experimental animals. It should not be used in pregnancy, particularly in early pregnancy, unless in the judgment of the physician the potential benefits outweigh the possible risks. Cytoxan is excreted in breast milk and breast-feeding should be terminated prior to institution of Cytoxan therapy.

Patients, male or female, capable of conception ordinarily should be advised of the mutagenic potential of Cytoxan. Adequate methods of contraception appear desirable for such patients receiving Cytoxan.

PRECAUTIONS

Cytoxan should be given cautiously to patients with any of the following conditions.

1. Leukopenia
2. Thrombocytopenia
3. Tumor cell infiltration of bone marrow
4. Previous X-ray therapy
5. Previous therapy with other cytotoxic agents
6. Impaired hepatic function
7. Impaired renal function

Because Cytoxan may exert a suppressive action on immune mechanisms, the interruption or modification of dosage should be considered for patients who develop bacterial, fungal or viral infections. This is especially true for patients receiving concomitant steroid therapy and perhaps those with a recent history of steroid therapy, since infections in some of these patients have been fatal. Varicella-zoster infections appear to be particularly dangerous under these circumstances.

ADVERSE REACTIONS

Secondary Neoplasia. Secondary malignancies have developed in some patients treated with cyclophosphamide alone or in association with other antineoplastic drugs and/or modalities. These malignancies most frequently have been urinary bladder, myeloproliferative, and lymphoproliferative malignancies. Secondary malignancies most frequently have developed in the cyclophosphamide-treated patients with primary myeloproliferative and lymphoproliferative malignancies and primary nonmalignant diseases in which immune processes are believed to be involved pathologically. In some cases, the secondary malignancy was detected up to several years after cyclophosphamide treatment was discontinued. The secondary urinary bladder malignancies generally have occurred in patients who previously developed hemorrhagic cystitis (see Genitourinary under Adverse Reactions). Although no cause-effect relationship has been established between cyclophosphamide and the development of malignancy in humans, the possibility of secondary malignancy, based on available data, should be considered in any benefit-to-risk assessment for the use of the drug.

Hematopoietic. Leukopenia is an expected effect and ordinarily is used as a guide to therapy. Thrombocytopenia or anemia may occur in a few patients. These effects are almost always reversible when therapy is interrupted.

Gastrointestinal. Anorexia, nausea, or vomiting are common and related to dose as well as individual susceptibility. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration and jaundice occurring during therapy.

Genitourinary. Sterile hemorrhagic cystitis can result from the administration of Cytoxan. **This can be severe, even fatal, and is probably due to metabolites in the urine.** Nonhemorrhagic cystitis and/or fibrosis of the bladder also have been reported to result from Cytoxan administration. Atypical epithelial cells may be found in the urinary sediment. **Ample fluid intake and frequent voiding help to prevent the development of cystitis,** but when it occurs it is ordinarily necessary to interrupt Cytoxan therapy. Hematuria usually resolves spontaneously within a few days after Cytoxan therapy is discontinued, but may persist for several months. In severe cases replacement of blood loss may be required. The application of electrocautery to telangiectatic areas of the bladder and diversion of urine flow have been successful methods used in treatment of protracted cases. Cryosurgery has also been used. (See also Secondary Neoplasia under Adverse Reactions.) Nephrotoxicity, including hemorrhage and clot formation in the renal pelvis, have been reported.

Gonadal suppression, resulting in amenorrhea or azoospermia, has been reported in a number of patients treated with cyclophosphamide and appears to be related to dosage and duration of therapy. This side effect, possibly irreversible, should be anticipated in patients treated with Cytoxan. It is not known to what extent Cytoxan may affect prepuberal gonads. Fibrosis of the ovary following Cytoxan therapy has been reported also.

Integument. It is ordinarily advisable to inform patients in advance of possible alopecia, a frequent complication of Cytoxan therapy. Regrowth of hair can be expected although occasionally the new hair may be of a different color or texture. The skin and fingernails may become darker during therapy. Non-specific dermatitis has been reported to occur with Cytoxan.

Pulmonary. Interstitial pulmonary fibrosis has been reported in patients receiving high doses of Cytoxan over a prolonged period.

DOSAGE AND ADMINISTRATION

Chemotherapy with Cytoxan, as with other drugs used in cancer chemotherapy, is potentially hazardous and fatal complications can occur. It is recommended that it be administered only by physicians aware of the associated risks. Therapy may be aimed at either induction or maintenance of remission.

Induction Therapy. The usual initial intravenous loading dose for patients with no hematologic deficiency is 40–50 mg/kg. This total initial intravenous loading dose usually is given in divided doses over a period of two to five days.

Patients with any previous treatment that may have compromised the functional capacity of the bone marrow, such as X ray or cytotoxic drugs, and patients with tumor infiltration of the bone marrow may require reduction of the initial loading dose by 1/3 to 1/2.

A marked leukopenia is usually associated with the above doses, but recovery usually begins after 7–10 days. The white blood cell count should be monitored closely during induction therapy.

If initial therapy is given orally, a dose of 1–5 mg/kg/day can be administered depending on tolerance by the patient.

Maintenance Therapy. It is frequently necessary to maintain chemotherapy in order to suppress or retard neoplastic growth. A variety of schedules has been used:

(1) 1–5 mg/kg p.o. daily
(2) 10–15 mg/kg i.v. every 7–10 days
(3) 3–5 mg/kg i.v. twice weekly

Unless the disease is unusually sensitive to Cytoxan, it is advisable to give the largest maintenance dose that can be reasonably tolerated by the patient. The total leukocyte count is a good objective guide for regulating the maintenance dose. Ordinarily a leukopenia of 3000-4000 cells/cu. mm. can be maintained without undue risk of serious infection or other complications.

Preparation and Handling of Solutions. Cytoxan for Injection should be prepared for parenteral use by adding **Sterile Water for Injection, U.S.P.** or **Bacteriostatic Water for Injection, U.S.P. (paraben preserved only)** to the vial and shaking to dissolve. Use 5 ml. for the 100-mg. vial, 10 ml. for the 200-mg. vial, or 25 ml. for the 500-mg. vial. Solutions of Cytoxan for Injection may be injected intravenously, intramuscularly, intraperitoneally or intrapleurally or they may be infused intravenously in Dextrose Injection, U.S.P. (5% dextrose) or Dextrose and Sodium Chloride Injection, U.S.P. (5% dextrose and 0.9% sodium chloride). These solutions should be used within 24 hours if stored at room temperature or within 6 days if stored under refrigeration. Cytoxan for Injection does not contain an antimicrobial agent and **care must be taken to insure the sterility of prepared solutions.**

Extemporaneous liquid preparations of Cytoxan for oral administration may be prepared by dissolving Cytoxan for Injection in Aromatic Elixir, U.S.P. Such preparations should be stored under refrigeration and used within 14 days.

OVERDOSAGE

No specific antidote for Cytoxan is known. Management of overdosage would include general supportive measures to sustain the patient through any period of toxicity that might occur.

HOW SUPPLIED

Cytoxan® (cyclophosphamide) for Injection. With sodium chloride.
NDC 0087-0500-01 100 mg vials, cartons of 12
NDC 0087-0501-01 200 mg vials, cartons of 12
NDC 0087-0502-01 500 mg vials, cartons of 12

Cytoxan® (cyclophosphamide) tablets.
NDC 0087-0503-01 50 mg, bottles of 100
NDC 0087-0503-02 50 mg, bottles of 1000
NDC 0087-0503-03 50 mg, Unit Dose cartons of 100
NDC 0087-0504-01 25 mg, bottles of 100

REFERENCES

References on selected topics and a physician's brochure are available by writing to: Medical Affairs Department, Mead Johnson Pharmaceutical Division, Evansville, Indiana 47721.

Mead Johnson PHARMACEUTICAL DIVISION

© 1979 Mead Johnson & Company • Evansville, Indiana 47721 U.S.A. MJL 9-4441

INDEX TO ADVERTISERS

PHARMACEUTICAL SUPPLIES

Amersham Corporation
  Ibrin 74A,75A
Beecham Laboratories
  Ticar ....56A thru 58A
Boehringer Ingelheim Limited
  Torecan 2A,3A
Breon Laboratories, Inc.
  Marcaine 76A,77A
Bristol Laboratories
  Cefadyl ....22A thru 24A
  Kantrex..................... 46A,47A
Burroughs Wellcome Company
  Empirin Compound c Codeine ..Cover IV

Eaton Laboratories
  Vivonex..................... 10A,11A
Endo Laboratories, Inc.
  Nubain ....35A thru 40A
  Percodan .... 82A,Cover III
Knoll Pharmaceuticals
  Dilaudid .... Cover II
Eli Lilly & Company
  Mandol ....63A thru 66A
Mc Neil Laboratories
Tylox 67A
Mead Johnson Nutritional Division
  Sustacal 45A
Mead Johnson Pharmaceutical Division
  Cytoxin ....78A thru 80A
  Megace..................27A thru 30A
Organon Pharmaceuticals
  Deca Durabolin 14A,15A
Parke Davis & Company
  Chloromycetin .... 6A thru 8A
Pfizer Laboratories
  Vistaril IM 50A,51A,52A
Roerig Division of Pfizer Pharmaceuticals
  Geopen..................... 70A,71A

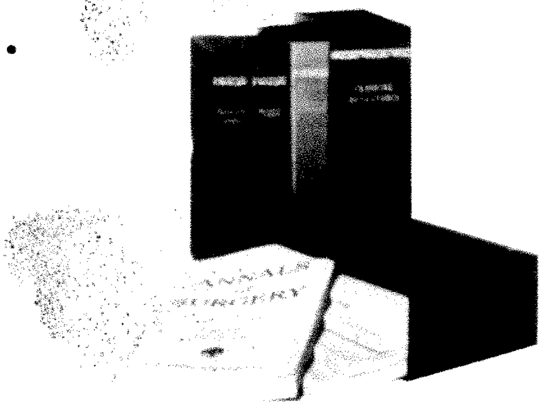
U S V Laboratories
MVI 72A, 73A
Viobin Corporation
Viokase 26A
Winthrop Laboratories
  Talwin 50.................60A thru 62A
  Talwin Injectable ....42A thru 44A

SUPPLIES & EQUIPMENT

Ethicon, Inc.
  Prolene Sutures 41A
  Proximate Skin Stapler 68A,69A
W. L. Gore & Assoc.
  Gore Tex Vascular Grafts .17A thru 21A
Intermedics, Inc.
  Cyberlith.................32A thru 34A
Johnson & Johnson
  Dermilite II................... 54A,55A
Life Sciences, Inc.
  Pulse Volume Recorder 1A
Medasonics
  Versatone Doppler.................16A
3M Surgical Products Division
  Steri Strips Skin Closures..........31A
Ortho Diagnostics, Inc.
  Chromogenic Assay III 25A
Purdue Frederick
  Betadine Surgical Products.......... 4A
Reed & Carnrick
  Proctofoam 48A,49A

MISCELLEANOUS

Grady Memorial Hospital............21A
Harper Row & Company, Publishers .72A
J. B. Lippincott Company....... 52A,53A
58A,59A,75A,82A
Maryland General Hospital..........21A
Univ. of Cinn. Coll. of Med...........46A



PRESERVE and PROTECT YOUR COPIES OF ANNALS of SURGERY

Now, your journals can become a handsome addition to your professional library.

These file boxes are designed and custom-made to keep your copies orderly, readily accessible and clean.

Durable book-binder's board covered with scuff-resistant, washable Leathertex. Lettering embossed in 23-Karat gold leaf.

Jesse Jones Box Corp. (since 1843)
Dep't. JBLA—Phila., Pa. 19141

Gentlemen: Kindly send me:
Reasonably priced, too. Only $4.95 ea. ☐
3 for $14.00 ☐ 6 for $24.00 ☐

Add $1.00 postage per file for orders outside the U.S.

☐ Check enclosed (Make check payable to: Jesse Jones Box Corp., Box 5120, Phila., Pa. 19141)

Name ______________________
Address ______________________
City/State/Zip ______________________

Shipped postpaid U.S. only. Satisfaction unconditionally guaranteed or your money back.

Tablets
PERCODAN®
oxycodone with APC ©II

Tablets
PERCODAN®-Demi
oxycodone with APC ©II

Brief Summary of Prescribing Information

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN* and PERCODAN*-Demi, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN* and PERCODAN*-Demi are subject to the Federal Controlled Substances Act

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN* and PERCODAN*-Demi should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN* and PERCODAN*-Demi may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN* and PERCODAN*-Demi should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN* should not be administered to children. PERCODAN*-Demi, containing half the amount of oxycodone, can be considered

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN* and PERCODAN*-Demi or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN* and PERCODAN*-Demi should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCODAN* and PERCODAN*-Demi are given orally

PERCODAN* The usual adult dose is one tablet every 6 hours as needed for pain

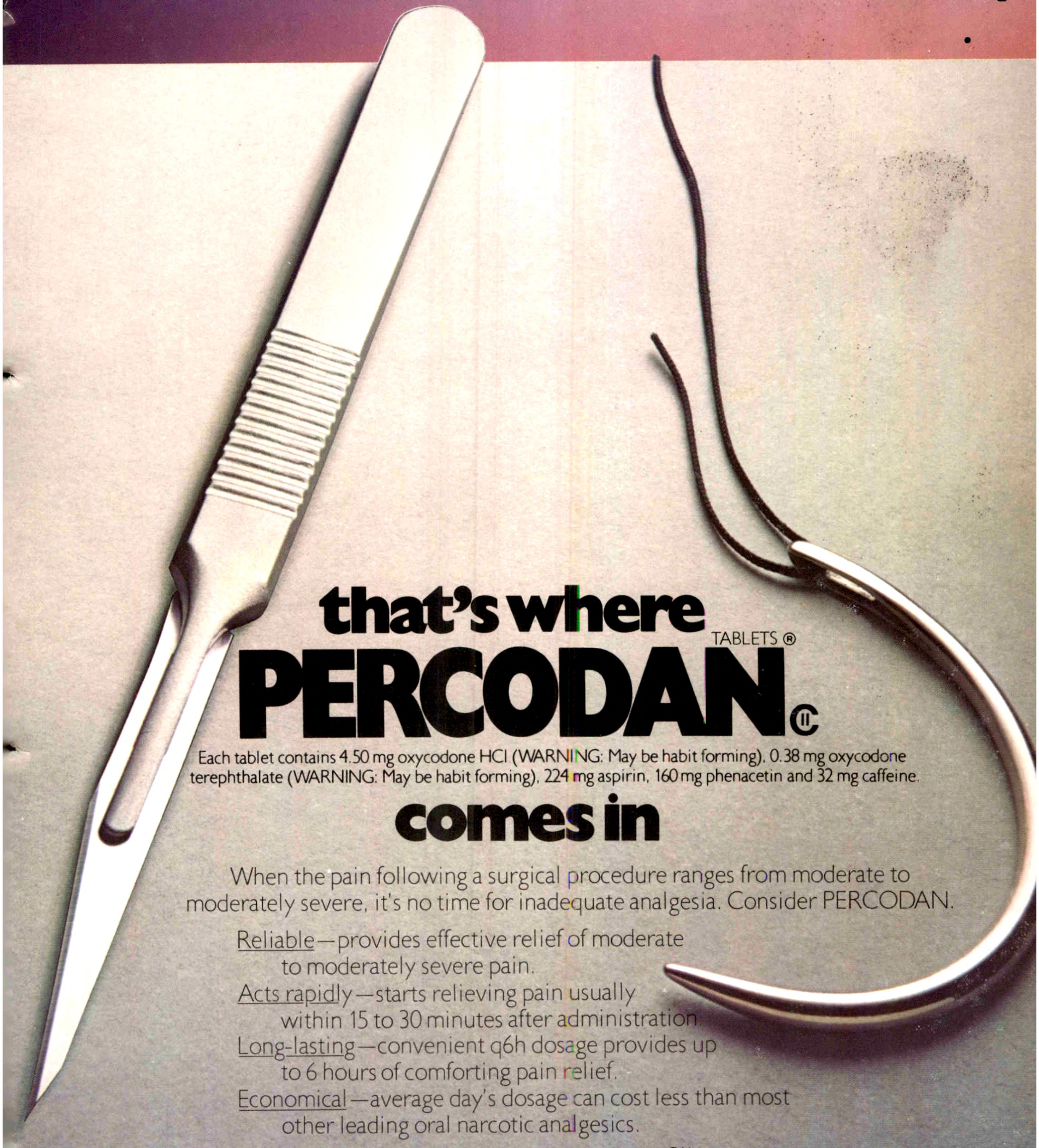
PERCODAN*-Demi Adults—One or two tablets every six hours. Children 12 years and older—One-half tablet every six hours. Children 6 to 12 years—One-quarter tablet every six hours. PERCODAN*-Demi is not indicated for children under 6 years of age.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN* and PERCODAN*-Demi may be additive with that of other CNS depressants. See WARNINGS

Aspirin may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

DEA Order Form Required. 6074-1/6078-1BS

Endo Inc.
Manati, Puerto Rico
DUPONT
Subsidiary of Endo Laboratories Inc.
Subsidiary of the DuPont Company



Between an I and D and a herniorrhaphy, there's a lot of room for pain...

that's where

PERCODAN TABLETS ® CII

Each tablet contains 4.50 mg oxycodone HCl (WARNING: May be habit forming), 0.38 mg oxycodone terephthalate (WARNING: May be habit forming), 224 mg aspirin, 160 mg phenacetin and 32 mg caffeine.

comes in

When the pain following a surgical procedure ranges from moderate to moderately severe, it's no time for inadequate analgesia. Consider PERCODAN.

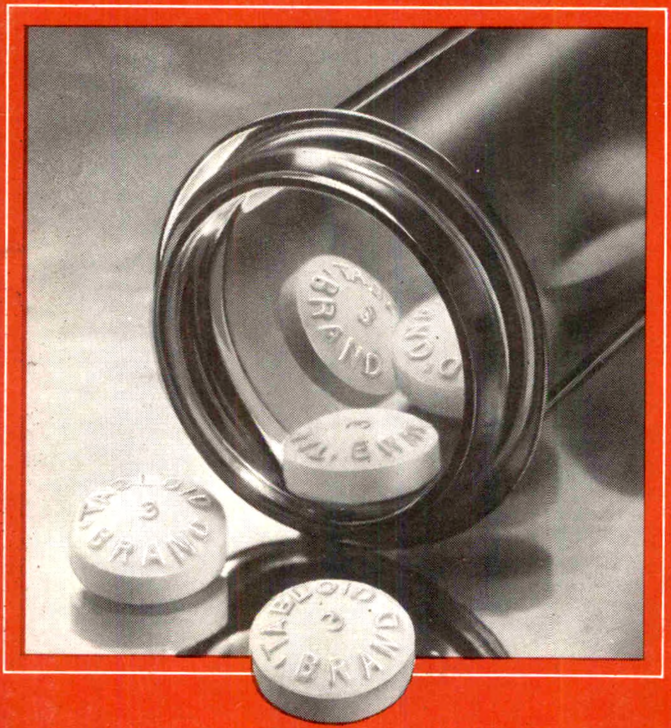
Reliable—provides effective relief of moderate to moderately severe pain.
Acts rapidly—starts relieving pain usually within 15 to 30 minutes after administration.
Long-lasting—convenient q6h dosage provides up to 6 hours of comforting pain relief.
Economical—average day's dosage can cost less than most other leading oral narcotic analgesics.

and when less narcotic is needed **PERCODAN®-Demi** Tablets CII

Each tablet contains 2.25 mg oxycodone HCl (WARNING: May be habit forming), 0.19 mg oxycodone terephthalate (WARNING: May be habit forming), 224 mg aspirin, 160 mg phenacetin and 32 mg caffeine.

Please see opposite page for brief summary of prescribing information.

PERCODAN is a registered trademark of Endo Inc.



EMPIRIN® COMPOUND
c̄ CODEINE

Each tablet contains: aspirin, 227 mg; phenacetin, 162 mg; and caffeine, 32 mg; plus codeine phosphate in one of the following strengths: #4—60 mg (gr 1); #3—30 mg (gr ½); #2—15 mg (gr ¼); and #1—7.5 mg (gr ⅛), (Warning—may be habit-forming). C III

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

Rec.
4.2.80

SEPTEMBER 1979 • VOL. 190, NO. 3
ISSN 0003-4932 ANSUA5

ANNALS of SURGERY

A Monthly Review of
Surgical Science and Practice
Since 1885

September and October numbers contain papers delivered at
THE 99th ANNUAL SESSION
of the
AMERICAN SURGICAL ASSOCIATION
Hot Springs, Virginia, April 26–28, 1979

LIBRARY

J. B. LIPPINCOTT COMPANY
PHILADELPHIA • TORONTO

Oral Dilaudid®

hydromorphone HCl CII

The first step after injectables in post-op analgesia.

Description: Dilaudid is hydromorphone, a hydrogenated ketone of morphine.
Indications: For relief of moderate to severe pain.
Contraindications: Suspected increased intracranial pressure, status asthmaticus.
Warnings: May be habit forming with a potential for addiction equivalent to morphine in equi-analgesic doses. Tolerance may also occur. As with all narcotics, use in early pregnancy only when expected benefits outweigh risks.
Adverse Effects: Nausea, vomiting, diarrhea, constipation, anorexia and somnolence may occur although unlikely with appropriate dose selection.
Dosage and Administration: Dosage must be individualized. The usual adult dose is 2 mg every 4-6 hours, as necessary, for moderate to moderately severe pain. For more severe pain, 3-4 mg or more every 4-6 hours, as necessary, may be required.
Treatment of Overdosage: If overdosage is treated within an hour, emesis and gastric lavage should be attempted. Special attention should be given to respiration and, if depression occurs, it may be antagonized by the use of naloxone hydrochloride (Narcan®)—Endo, nalorphine hydrochloride (Nalline®)—Merck Sharp & Dohme or levallorphan tartrate (Lorfan®)—Roche, as recommended by the manufacturer. Other supportive measures should be applied when indicated.
How Supplied: Dilaudid HCl color coded tablets (NOT FOR INJECTION) imprinted with K logo on one side and potency on other side as follows: green—1 mg; orange—2 mg; pink—3 mg and yellow—4 mg. Available in: 1 mg—bottles of 100 (NDC #0044-1021-02), 2 mg—bottles of 100 (NDC #0044-1022-02) and 500 (NDC #0044-1022-03), 3 mg—bottles of 100 (NDC #0044-1023-02), 4 mg—bottles of 100 (NDC #0044-1024-02) and 500 (NDC #0044-1024-03).

Knoll Pharmaceutical Company
Whippany, New Jersey 07981

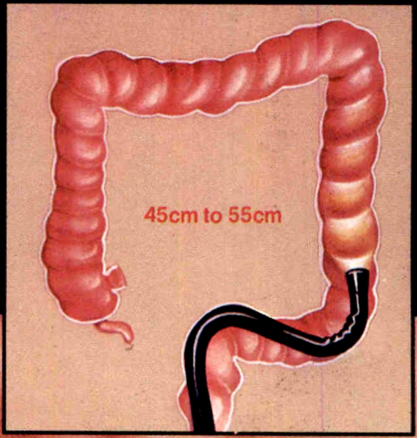
Member Company, Certified Medical
Representative Institute, Inc.

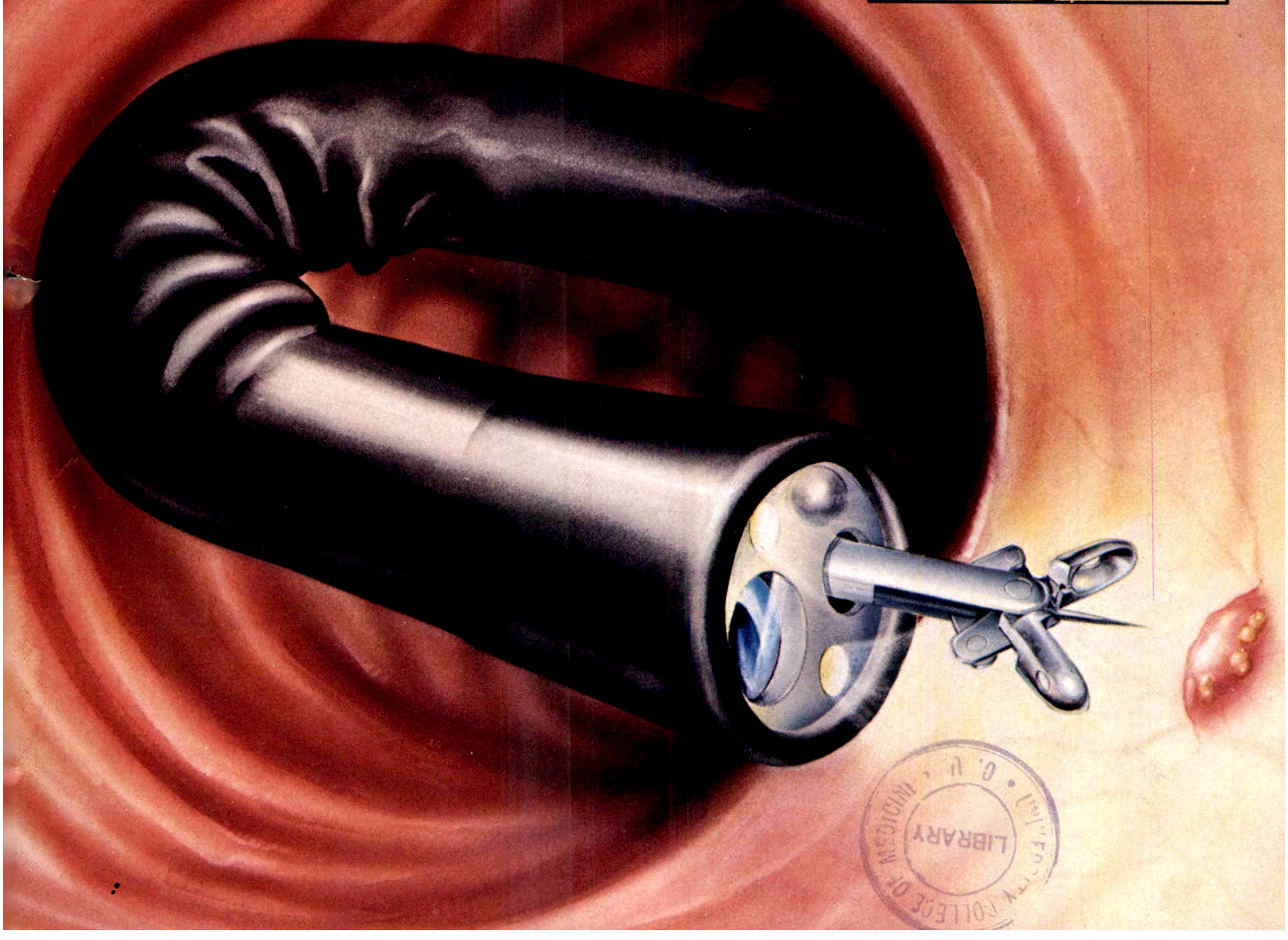
diagnostic yield of our impressive instrument.
Write American Cystoscope Makers Inc.,
300 Stillwater Avenue, Stamford, CT 06902.

ACMI

An ACMI Sigmoidoscope can put you here.

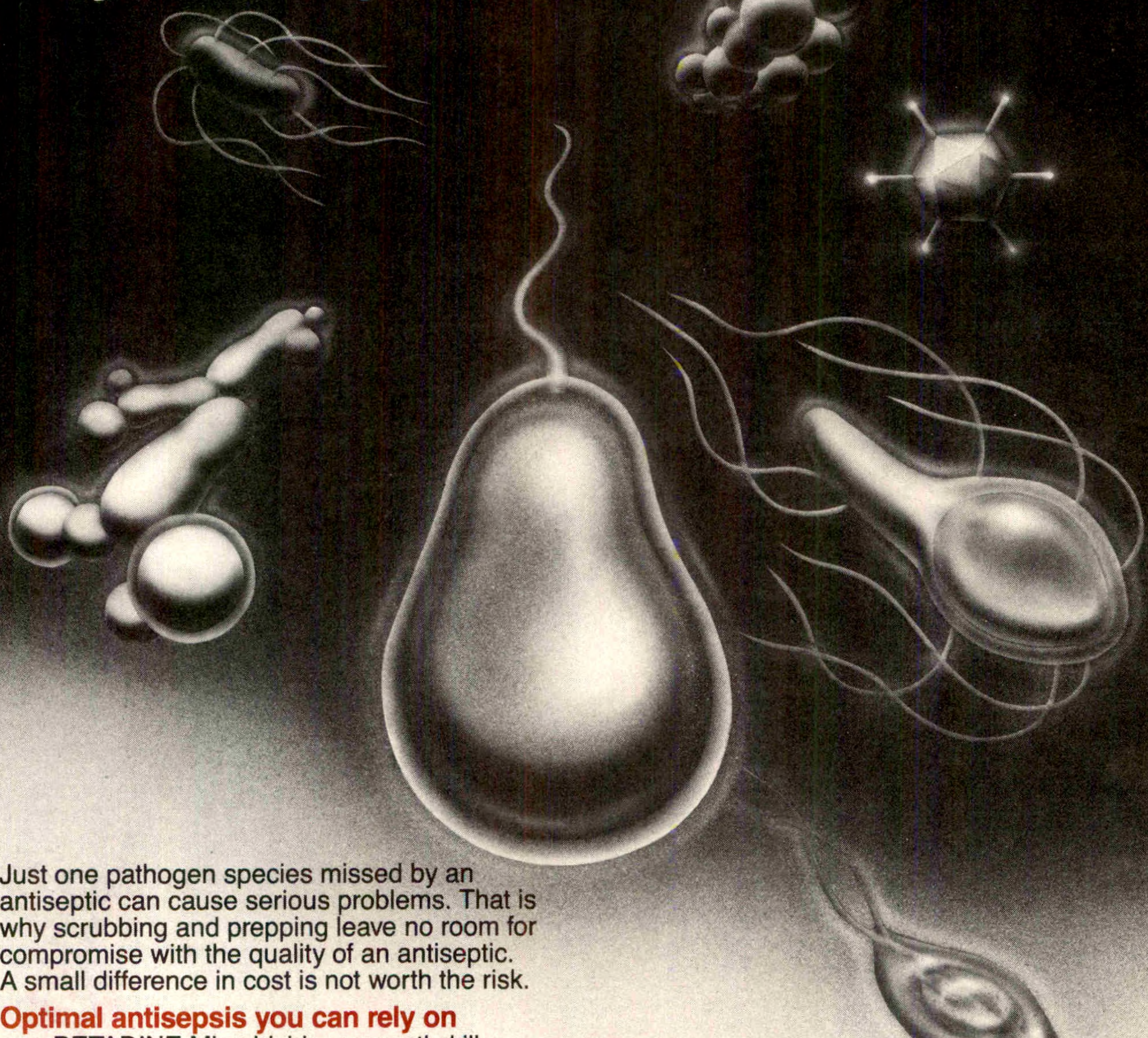
...in your own office





LIBRARY
U. C. • UNIVERSITY COLLEGE OF MEDICINE

Pathogens don't compromise. Why should you?



Just one pathogen species missed by an antiseptic can cause serious problems. That is why scrubbing and prepping leave no room for compromise with the quality of an antiseptic. A small difference in cost is not worth the risk.

Optimal antisepsis you can rely on

BETADINE Microbicides promptly kill gram-positive and gram-negative bacteria, fungi, viruses, protozoa and yeasts.

BETADINE Microbicides have been documented specifically by name—and in the same formulations you employ in practice—in over 650 published reports encompassing thousands of clinical procedures.

BETADINE Microbicides were also chosen by NASA for disinfection procedures in Apollo splashdowns and in the Skylab mission.

BETADINE Microbicides for surgical confidence

_____ BETADINE Surgical Scrub*—for surgical scrubbing and patient degerming.

_____ BETADINE Solution or BETADINE Aerosol Spray—for patient prepping and postoperative antisepsis on incisions.

Uncompromising antisepsis for scrubbing and prepping

BETADINE® Surgical Scrub
BETADINE® Solution
BETADINE® Aerosol Spray

*In the rare instances of local irritation or sensitivity, discontinue use by the individual.

Purdue Frederick

©Copyright 1979, The Purdue Frederick Company/Norwalk, CT 06856

A9458 214679

Annals of Surgery

A Monthly Review of Surgical Science and Practice

Also the official publication of
THE AMERICAN SURGICAL ASSOCIATION
THE SOUTHERN SURGICAL ASSOCIATION
PHILADELPHIA ACADEMY OF SURGERY
NEW YORK SURGICAL SOCIETY

EDITORIAL AND ADVISORY BOARD

DAVID C. SABISTON, JR., M.D., *Chairman*
Durham, N.C.

J. WESLEY ALEXANDER, M.D.
Cincinnati, O.
WILLIAM A. ALTEMEIER, M.D.
Cincinnati, O.
W. GERALD AUSTEN, M.D.
Boston, Mass.
HENRY T. BAHNSON, M.D.
Pittsburgh, Pa.
WARREN H. COLE, M.D.
Asheville, N.C.
MICHAEL E. DE BAKEY, M.D.
Houston, Tex.
STANLEY J. DUDRICK, M.D.
Houston, Tex.
J. ENGLEBERT DUNPHY, M.D.
San Francisco, Calif.
PAUL A. EBERT, M.D.
San Francisco, Calif.
ERIC W. FONKALSRUD, M.D.
Los Angeles, Calif.
FRANK L. A. GERBODE, M.D.
San Francisco, Calif.
FRANK GLENN, M.D.
New York, N.Y.
FRASER N. GURD, M.D.
Ottawa, Canada
OLGA M. JONASSON, M.D.
Chicago, Ill.

WILLIAM P. LONGMIRE, JR., M.D.
Los Angeles, Calif.
LEONARD D. MILLER, M.D.
Philadelphia, Pa.
FRANCIS D. MOORE, M.D.
Boston, Mass.
WILLIAM H. MULLER, JR., M.D.
Charlottesville, Va.
JOHN S. NAJARIAN, M.D.
Minneapolis, Minn.
JONATHAN E. RHOADS, M.D.
Philadelphia, Pa.
PAUL S. RUSSELL, M.D.
Boston, Mass.
JOHN A. SCHILLING, M.D.
Seattle, Wash.
G. THOMAS SHIRES, M.D.
New York, N.Y.
HARRIS B. SHUMACKER, JR., M.D.
Indianapolis, Ind.
DAVID B. SKINNER, M.D.
Chicago, Ill.
FRANK C. SPENCER, M.D.
New York, N.Y.
SAMUEL A. WELLS, JR., M.D.
Durham, N.C.

Emeritus Members

William F. Rienhoff, Jr., Baltimore, Md., John D. Stewart, M.D., Boca Raton, Fla.

J. B. LIPPINCOTT COMPANY, *Publishers*
Philadelphia and Toronto

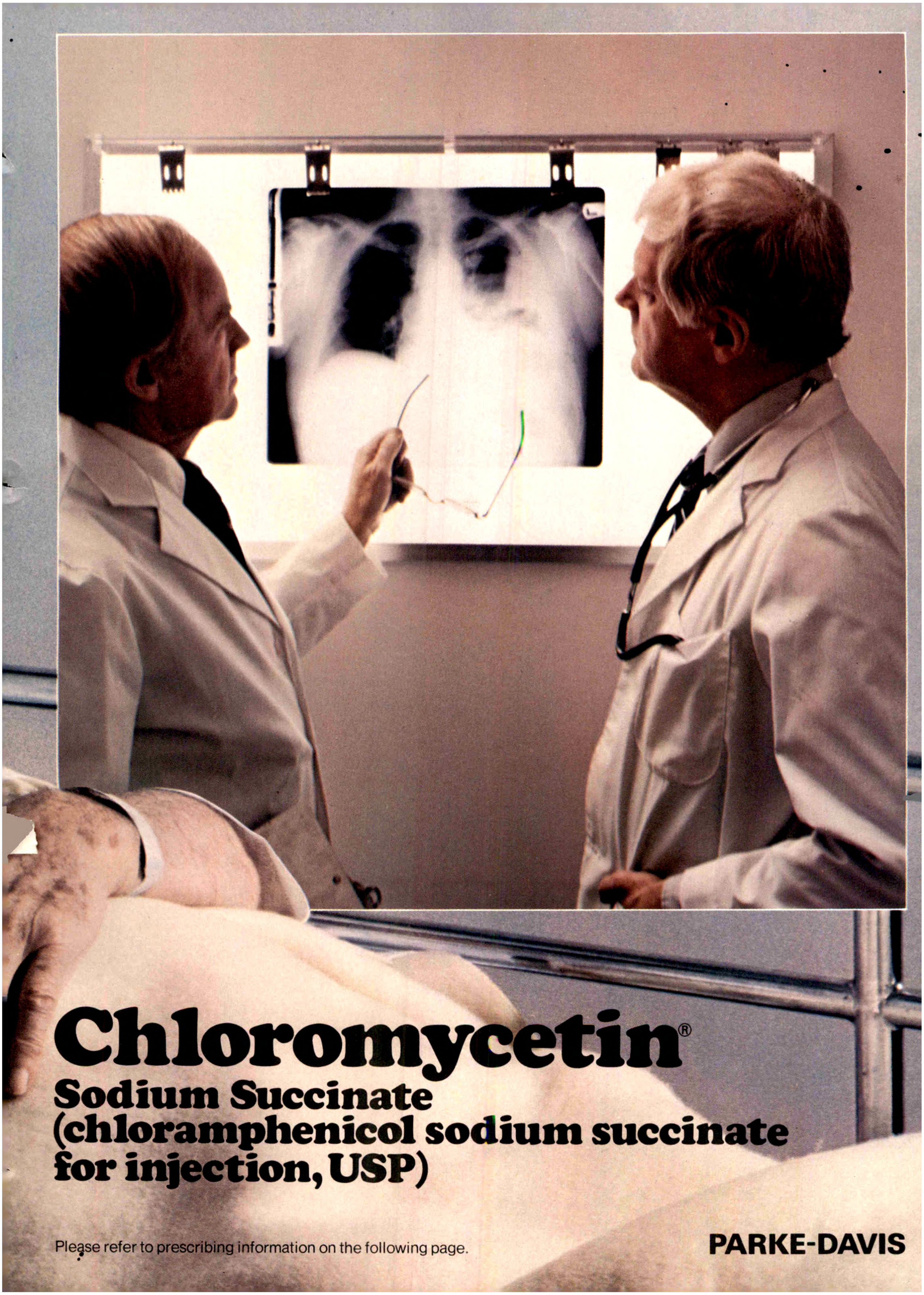
Annals of Surgery (ISSN 0003-4932) is published monthly for $29.00 per year for the United States and its possessions; resident rate (U.S. only) $21.00; all other countries $39.00; by J. B. Lippincott Co., East Washington Square, Philadelphia, PA 19105. Second-class postage paid at Philadelphia, PA and at additional mailing offices.
POSTMASTER: Send address changes to Annals of Surgery, J. B. Lippincott Co.,
East Washington Square, Philadelphia, PA.
Single copies $5.00. Copyright © 1979 J. B. Lippincott Co. Printed in U.S.A.

Valuable in serious gram-negative infections* (including anaerobic infections)

- lung abscess/empyema
- endocarditis
- septicemia/bacteremia
- deep-seated abscess
- brain abscess
- epiglottitis
- meningitis
- wound infections
- abdominal sepsis
- pelvic abscesses

Chloromycetin (chloramphenicol sodium succinate for injection, USP) is one antibiotic that consistently crosses the blood-brain barrier in effective concentrations. It has a remarkably broad spectrum that includes organisms within the designation of gram-negative and gram-positive, aerobic and anaerobic and, especially, many species of the anaerobes, such as *Bacteroides, Clostridium,* and *Peptostreptococcus,* responsible for serious infections. Used judiciously, Chloromycetin can save lives.

*Due to susceptible organisms, when less potentially hazardous therapeutic agents are ineffective or contraindicated.



Chloromycetin®
Sodium Succinate
(chloramphenicol sodium succinate
for injection, USP)
Please refer to prescribing information on the following page.
PARKE-DAVIS

Prescribing Information
Chloromycetin® Sodium Succinate
(chloramphenicol sodium succinate for injection, USP)
For intravenous administration

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the INDICATIONS section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

CHLORAMPHENICOL SODIUM SUCCINATE IS INTENDED FOR INTRAVENOUS USE ONLY. IT HAS BEEN DEMONSTRATED TO BE INEFFECTIVE WHEN GIVEN INTRAMUSCULARLY.

1. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for*, serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see INDICATIONS section).

Each gram (10 ml of a 10% solution) of chloramphenicol sodium succinate contains approximately 52 mg (2.25 mEq) of sodium

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group, and *Vibrio cholerae*. Chloramphenicol is particularly active against *Salmonella typhi* and *Hemophilus influenzae*. The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every six hours for eight doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/ml one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/ml after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/ml over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8 to 12% of the antibiotic excreted is in the form of free chloramphenicol, the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Because the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/ml in patients receiving divided doses of 50 mg/kg/day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

In accordance with the concepts in the WARNING box and this INDICATIONS section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present: *in vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by *in vitro* studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in the WARNING box above:

1. Acute infections caused by *S typhi**
   It is not recommended for the routine treatment of the typhoid carrier state.
2. Serious infections caused by susceptible strains in accordance with the concepts expressed above:
   a) *Salmonella* species
   b) *H influenzae*, specifically meningeal infections
   c) Rickettsia
   d) Lymphogranuloma-psittacosis group
   e) Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
   f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents
3. Cystic fibrosis regimens

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat, or as a prophylactic agent to prevent bacterial infection.*

PRECAUTIONS

1. Baseline blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.

3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

4. Excessive blood levels may result from administration of the recommended dosage to patients with impaired liver or kidney functions, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.

5. There are no studies to establish the safety of this drug in pregnancy.

6. Because chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).

7. Precaution should be used in therapy of premature and full-term infants to avoid gray syndrome toxicity (see **ADVERSE REACTIONS).** Serum drug levels should be carefully followed during therapy of the newborn infant.

8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed. A reversible type of bone marrow depression, which is dose-related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes, and leukopenia, and responds promptly to the withdrawal of chloramphenicol

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding (1) the size of the population at risk, (2) the total number of drug-associated dyscrasias, and (3) the total number of non-drug-associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis has been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the gray syndrome. One case of gray syndrome has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month-old infant. The following summarizes the clinical and laboratory studies that have been made on these patients.

a) In most cases, therapy with chloramphenicol had been instituted within the first 48 hours of life
b) Symptoms first appeared after three to four days of continued treatment with high doses of chloramphenicol
c) The symptoms appeared in the following order:
   (1) abdominal distention with or without emesis;
   (2) progressive pallid cyanosis;
   (3) vasomotor collapse, frequently accompanied by irregular respiration;
   (4) death within a few hours of onset of these symptoms.
d) The progression of symptoms from onset to exitus was accelerated with higher-dosage schedules.
e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/ml after repeated doses).
f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended dosages known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the intravenous form because adequate blood levels are achieved with chloramphenicol by mouth.

The following method of administration is recommended:

Intravenously as a 10% (100 mg/ml) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 ml of an aqueous diluent, such as water for injection or 5% dextrose injection.

DOSAGE

Adults

Adults should receive 50 mg/kg/day in divided doses at six-hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high dosages should be decreased as soon as possible. Adults with impairment of hepatic or renal functions or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under *Newborn Infants.*) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg/kg/day divided into four doses at six-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (eg., bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney functions may retain excessive amounts of the drug.

Newborn Infants

(See section titled Gray Syndrome under ADVERSE REACTIONS.)

A total of 25 mg/kg/day in four equal doses at six-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into four doses at six-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under 2 weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dosage of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

HOW SUPPLIED

N 0071-4057-03 (Steri-Vial® No. 57)
Chloromycetin (chloramphenicol) Sodium Succinate is supplied as a dried powder in Steri-Vials (rubber diaphragm-capped vials). When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per milliliter (1 g/10 ml). Available in packages of 10 vials
Chloromycetin, brand of chloramphenicol, Reg US Pat Off

RJ

PARKE-DAVIS

PD-JA-2284-1-P(10-78)

PARKE-DAVIS
Division of Warner-Lambert Company
Morris Plains, NJ 07950

---

*In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse

ANNALS OF SURGERY

Vol. 190 September 1979 No. 3

CONTENTS

265 **Presidential Address: The Unfinished Painting**
Oliver H. Beahrs, M.D., *Rochester, Minnesota*

274 **Glucose Requirements Following Burn Injury: Parameters of Optimal Glucose Infusion and Possible Hepatic and Respiratory Abnormalities Following Excessive Glucose Intake**
John F. Burke, M.D., *Robert R. Wolfe,* PH.D., *Charles J. Mullany,* M.D., *Dwight E. Mathews,* PH.D., *Dennis M. Bier,* M.D., *St. Louis, Missouri*

286 **Therapeutic Approaches to Anergy in Surgical Patients: Surgery and Levamisole**
Jonathan L. Meakins, M.D., *Nicholas V. Christou,* M.D., *Harry M. Shizgal,* M.D., *Lloyd D. MacLean,* M.D., *Quebec, Canada*

297 **Correlation Between Anergy and a Circulating Immunosuppressive Factor Following Major Surgical Trauma**
Gerard A. McLoughlin, M.D., *Andrew V. Wu,* M.D., *Inna Saporoschetz,* A.B., *Richard Nimberg,* D.M.D., *John A. Mannick,* M.D., *Boston, Massachusetts*

305 **Vasodilator Effects of the Sodium Acetate in Pooled Protein Fraction**
Gordon N. Olinger, M.D., *Paul H. Werner,* M.D., *Lawrence I. Bonchek,* M.D., *Lawrence E. Boerboom,* PH.D., *Milwaukee, Wisconsin*

312 **Surgical Treatment of Chronic Pancreatitis: Twenty-Two Years' Experience**
L. William Traverso, M.D., *Ronald K. Tompkins,* M.D., *Paul T. Urrea,* B.A., *William P. Longmire, Jr.,* M.D., *Los Angeles, California*

320 **Twenty Year Experience in Maxillocraniofacial Surgery: An Evaluation of Early Surgery on Growth, Function and Body Image**
Joseph E. Murray, M.D., *John B. Mulliken,* M.D., *Leonard B. Kaban,* D.M.D., *Myron Belfer,* M.D., *Boston, Massachusetts*

332 **Congenital Diaphragmatic Hernia: New Concept in Management**
Stephen J. Shochat, M.D., *Richard L. Naeye,* M.D., *W. D. A. Ford,* M.B., *Victor Whitman,* M.D., *M. Jeffrey Maisels,* M.D., *Hershey, Pennsylvania*

342 **The Fibrinolytic System: A Key to Tumor Metastasis?**
J. M. Malone, M.D., *S. L. Wangensteen,* M.D., *W. S. Moore,* M.D., *K. Keown,* M.A., *Tucson, Arizona*

350 **Enhanced Survival of Patients with Colon and Rectal Cancer is Based Upon Wide Anatomic Resection**
Warren E. Enker, M.D., *Urban Th. Laffer,* M.D., *George E. Block,* M.D., *Chicago, Illinois*

Now...enteral hyperalimentation by special delivery.

No pumps
Allows continuous gravity-flow administration.

Lightweight
Ambulatory patients can maneuver with more ease.

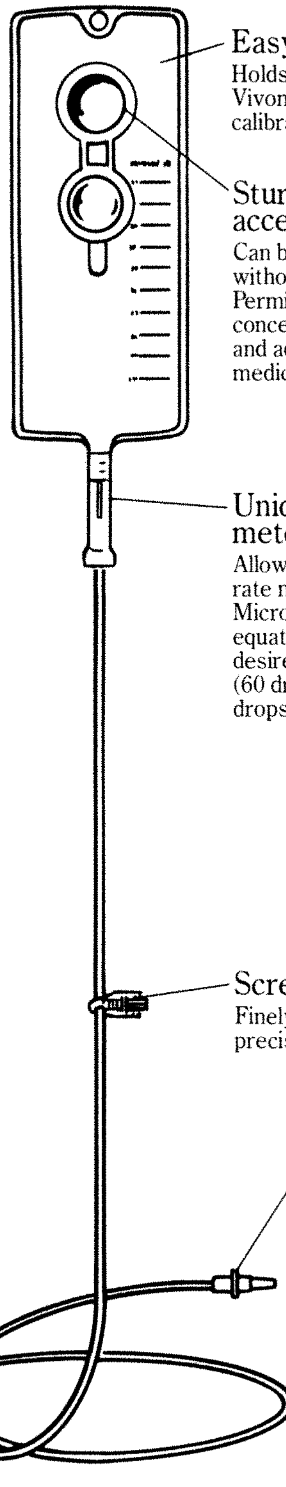
Eliminates jerry-rigging
A single component that's disposable. Saves time for the entire staff.

Economical
Just add Vivonex HN and a feeding tube.

Simple flow regulation

"The plastic bag administration set and a microdrip chamber permit accurate administration during a wide range of rates. The elimination of the need for an infusion pump renders the technique less expensive and cumbersome. The patients may be fully ambulatory while receiving therapy."[1]

Special... because it's a complete system.



Easy-to-fill pouch
Holds up to 1 liter of Vivonex HN; 100-ml calibrations add accuracy.

Sturdy pouch access
Can be opened and closed without weakening. Permits volume or concentration changes and addition of vitamins or medications.

Unique drip meter
Allows simple flow-rate monitoring. Microdrops/minute equate to ml/hr for desired flow rate (60 drops≈1 ml; 60 drops/min≈60 ml/hr).

Screw clamp
Finely threaded for precise adjustment.

Male Luer
Fits most small-caliber feeding tubes.

References: 1. Page CP, Ryan JA Jr, Haff RC: Continual catheter administration of an elemental diet. *Surg Gynecol Obstet* 142:184-188, 1976. *2.* Randall HT (ed): Nutrition and surgical patients. *Contemp Surg* 11(1):7-22, 1977. *3.* Blackburn GL, Bistrian BR: Nutritional care of the injured and/or septic patient. *Surg Clin North Am* 56:1195-1224, 1976.

Special... because it delivers Vivonex® HN.*

VIVONEX HN provides complete enteral nutrition with free amino acids. Being truly elemental, it requires minimal digestion and allows maximal absorption. The extremely low viscosity allows Vivonex HN to flow continuously, at *any* rate, without clogging.

"Increasingly, these diets are used in patients with fistulas, inflammatory bowel disease, partial obstruction, and malabsorption—states for which total parenteral nutrition was once considered most appropriate."[2]

VIVONEX HN—*the only elemental high nitrogen diet*—has "...a nitrogen to calorie ratio of 1:150—the best ratio for anabolism."[3] By continuous administration of Vivonex HN via the Vivonex Delivery System, the same positive nitrogen balance, weight gain, and accelerated wound healing can be achieved as with parenteral hyperalimentation, but without the catheter-induced thrombophlebitis, sepsis, and patient discomfort.

*Information on Vivonex HN usage and precautions accompanies the product and should be reviewed before use.

Norwich-Eaton Pharmaceuticals
Division of Morton-Norwich Products, Inc.
Norwich, NY 13815

VIVONEX®
DELIVERY SYSTEM

EV-8061

CONTENTS *Continued*

361 **Chinese Experience in the Surgical Treatment of Carcinoma of the Esophagus**
Wu Ying-K'Ai, Huang Kuo-Chun, People's Republic of China

366 **Specific Active Immunotherapy for Melanoma**
H. F. Seigler, M.D., *E. Cox, F. Mutzner, L. Shepherd, E. Nicholson, W. W. Shingleton, Durham, North Carolina*

373 **Histopathology in the Evaluation of Total Pancreatectomy for Ductal Carcinoma**
A. Francine Tryka, M.D., *John R. Brooks,* M.D., *Boston, Massachusetts*

382 **The Price of Weight Loss by Jejunoileal Shunt**
Mark M. Ravitch, M.D., *Robert E. Brolin,* M.D., *Pittsburgh, Pennsylvania*

392 **Gastric Partitioning for Morbid Obesity**
William G. Pace, M.D., *Edward W. Martin, Jr.,* M.D., *Ted Tetirick,* M.D., *Peter J. Fabri,* M.D., *Larry C. Carey,* M.D., *Columbus, Ohio*

401 **The Natural History and Surgical Significance of Hyperlipemic Abdominal Crisis**
Arnold Miller, M.B.CH.B., *Robert S. Lees,* M.D., *Martha A. McCluskey,* R.N., *Andrew L. Warshaw,* M.D., *Boston, Massachusetts*

409 **Surgical Decision Making: The Reliability of Clinical Judgment**
Ira M. Rutkow, M.D., *Alan M. Gittelsohn,* PH.D., *George D. Zuidema,* M.D., *Baltimore, Maryland*

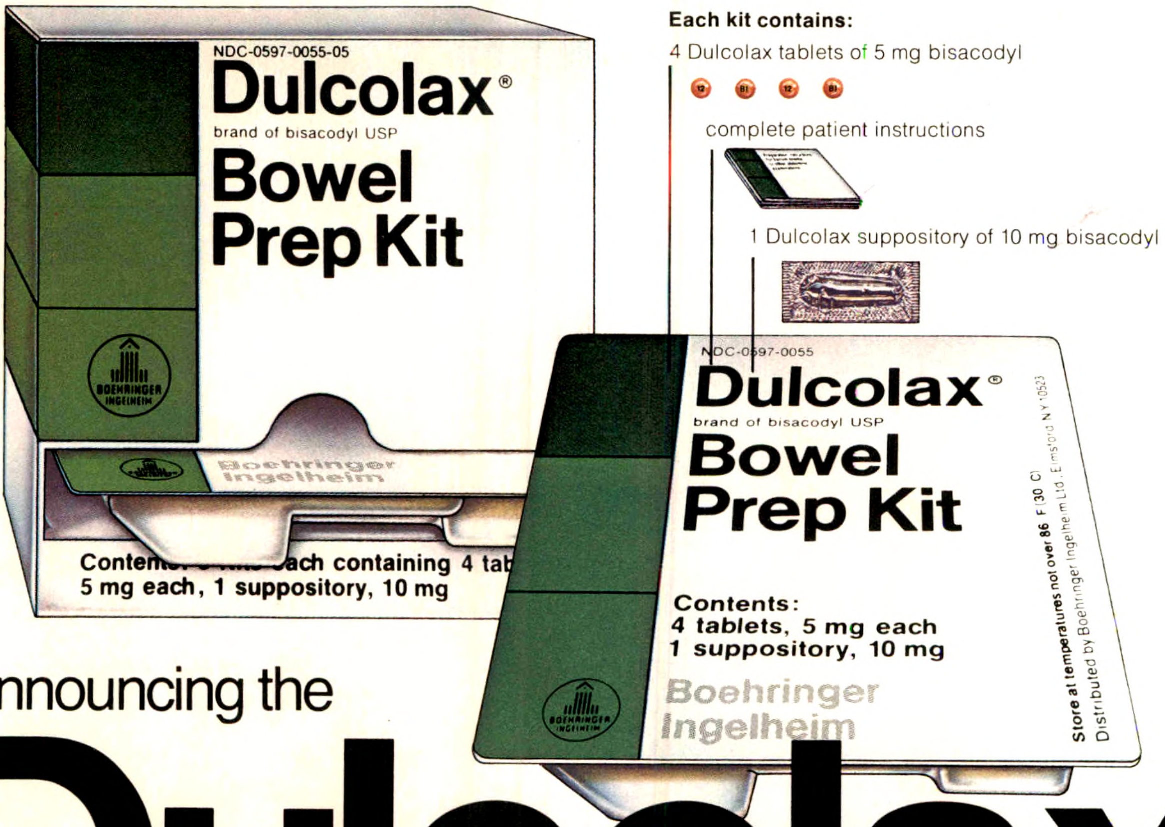
420 **Book Reviews**

- **Compact...**easy to store...all in a sealed, plastic container
- **Versatile...**easily snaps onto the top of a magnesium citrate bottle...can be used with other saline cathartics or with castor oil
- **Economical...**suggested retail price is less than most other kits
- **Convenient...**for nursing staff or the outpatient. Sold in a handy dispenser of 5.

With the Dulcolax Bowel Prep Kit plus magnesium citrate "...the reexamination rate of patients because of poorly cleansed colons has fallen to approximately 1 percent of all barium enema studies."[1]

[1] Sorrentino A P et al. Am J Hosp Pharm *26*:432-435, 1969.

Boehringer Ingelheim Ltd.
Ridgefield, CT 06877


NDC-0597-0055-05
Dulcolax®
brand of bisacodyl USP
Bowel
Prep Kit
Boehringer Ingelheim
Contents: ... each containing 4 tab
5 mg each, 1 suppository, 10 mg
NDC-0597-0055
Dulcolax®
brand of bisacodyl USP
Bowel
Prep Kit
Contents:
4 tablets, 5 mg each
1 suppository, 10 mg
Boehringer
Ingelheim
Store at temperatures not over 86 F (30 C)
Distributed by Boehringer Ingelheim Ltd., Elmsford, N.Y. 10523
Each kit contains:
4 Dulcolax tablets of 5 mg bisacodyl
complete patient instructions
1 Dulcolax suppository of 10 mg bisacodyl

Announcing the

Dulcolax®

Bowel Prep Kit

Notice to Contributors and Subscribers

ANNALS OF SURGERY is a monthly journal which considers for publication original articles in the field of surgery. It is the oldest continuously published journal in the English language solely devoted to the surgical sciences. The Editorial Board considers only papers judged to offer significant contributions to the advancement of surgical knowledge.

CONTRIBUTIONS. Four typed copies of the manuscript and four copies of the illustrations should be sent prepaid to the Chairman of the Editorial Board of ANNALS OF SURGERY:

David C. Sabiston, Jr., M.D.
Annals of Surgery
Department of Surgery
Duke University Medical Center
Durham, North Carolina 27710

Manuscripts and references should be typed double spaced on one side of 8½ × 11 paper leaving wide margins. Authors should retain a complete copy of the manuscript including illustrations in the event that the manuscripts are lost in the mail. A complete address for reprint requests should be included on the title page together with the name of the institution from which the work is being published.

An abstract of *not more than 200 words* should be placed at the beginning of the manuscript. It should accurately reflect the paper and provide readers with a reliable impression of the contents and conclusions of the work.

Digits one to ten should be spelled out, except when used for units of measurement (time, weight, volume, dosage, degrees) percentage, or when decimals are involved; for numbers above ten, numerals should be used. Dorland's Medical Dictionary and Webster's International Dictionary may be used as standard references. Scientific names for drugs should be used when possible. Copyright or trade names of drugs should be capitalized. Units of measurement should be expressed in the metric system. Temperature should be expressed in degrees centigrade. All contributions should be submitted in English.

Black and white illustrations will be reproduced free of charge, but the publisher reserves the right to establish a reasonable limit upon the number supplied. Color illustrations will be published at the author's expense. Black and white photographs should be in the form of glossy prints. Line and wash drawings should be black on white paper, with lettering in black india ink or transfer lettering, large enough to be readable after necessary reduction. Large or bulky illustrations should be accompanied by smaller glossy reproductions of the same. Illustrations should be numbered, the tops indicated, and the author's name and the title of the article in brief appear on the back. A separate typewritten sheet of legends for the illustrations should be supplied.

An alphabetical list of numbered references should appear at the end of the manuscript with corresponding numbers in the text. All references should be specifically mentioned in the body of the manuscript. The list of references should be *selective* with not more than 20 references except under unusual circumstances. References should conform to the style of the Index Medicus.

McNamara, J. J., Molot, M. D. and Stremple, J.: Changes in Some Physical Properties of Stored Blood. Ann. Surg., 174:58, 1971.

PUBLISHER'S NOTICES

CHANGE OF ADDRESS: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the journal.

Copies will not be replaced without charge unless we receive a request within 60 days of the mailing in the U. S. or within 90 days in all other countries.

BUSINESS ADDRESS: Subscriptions, reprints, advertising, and all business communications should be addressed to:

ANNALS OF SURGERY
J. B. Lippincott Co.
East Washington Square
Philadelphia, Pa. 19105

Published Monthly. Subscription Rates $27.00 per year in United States and possessions; all other countries $37.00. All prices include postage. Single issues $5.00. Rate for Residents, U.S. only, $19.00.

The publishers accept no responsibility for opinions expressed by contributors.

POSTOPERATIVE PAIN

prompt narcotic/analgesic relief without A.P.C.

The principal analgesic ingredient, oxycodone, is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine. The analgesic effect of oxycodone begins within 10 to 15 minutes after oral administration, peaks at 45 minutes, and persists for 3 to 6 hours.[†] Acetaminophen, a non-narcotic analgesic, complements the pain relief provided by oxycodone.

Summary of Prescribing Information

Contraindications: Hypersensitivity to oxycodone or acetaminophen.

Warnings: *Drug dependence:* Oxycodone can produce drug dependence of the morphine type and may be abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration; prescribe and administer with same caution appropriate to other oral narcotic-containing medications. Subject to the Federal Controlled Substances Act.
Usage in ambulatory patients: Caution patients that oxycodone may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.
Interaction with other Central Nervous System depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) with TYLOX capsules may exhibit additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.
Usage in pregnancy: Safe use not established. Should not be used in pregnant women unless potential benefits outweigh possible hazards.
Usage in children: Should not be administered to children.

Precautions: *Head injury and increased intracranial pressure:* The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.
Acute abdominal conditions: TYLOX capsules or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.
Special risk patients: Administer with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Adverse Reactions: *Most frequent:* Lightheadedness, dizziness, sedation, nausea and vomiting; more prominent in ambulatory than non-ambulatory patients; some of these reactions may be alleviated if the patient lies down. *Others:* euphoria, dysphoria, constipation, skin rash and pruritus.

Dosage and Administration: Dosage should be adjusted according to severity of pain and response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. TYLOX capsules are given orally. Usual adult dose is one capsule every 6 hours as needed for pain.

Drug Interactions: CNS depressant effects may be additive with that of other CNS depressants. See Warnings.
Caution: Federal law prohibits dispensing without prescription.
For information on symptoms/treatment of overdosage, see full prescribing information.
Full directions for use should be read before administering or prescribing.

[†] Halpern, L.M., and Bonica, J.J., "Analgesics," in Modell, W., ed. Drugs of Choice 1976-1977, St. Louis, The C.V. Mosby Co., 1976, p. 213. 0775

TYLOX® CII

CAPSULES

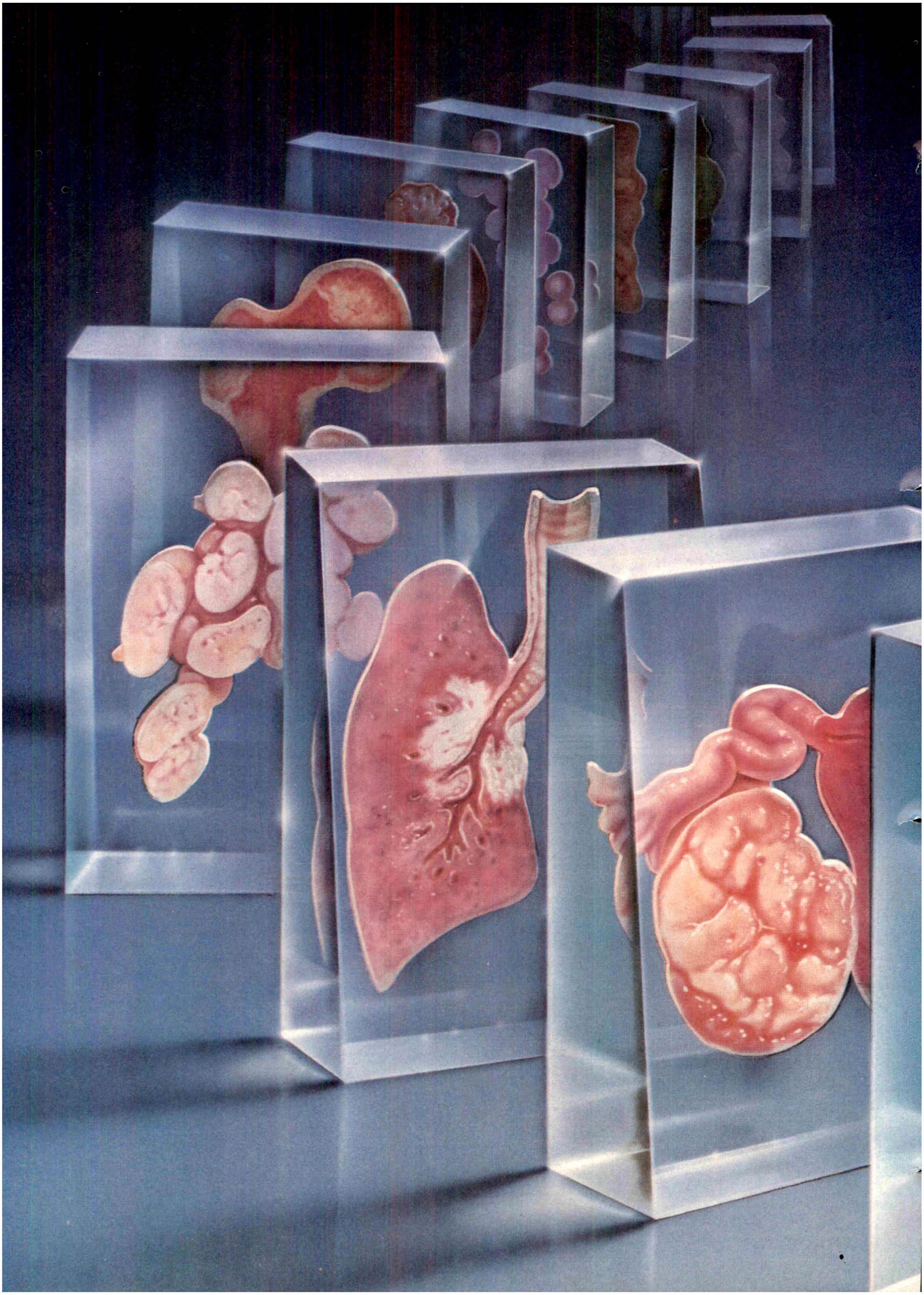
oxycodone HCl* 4.5 mg,
oxycodone terephthalate* 0.38 mg,
acetaminophen 500 mg

***Warning:** May be habit forming.

McNEIL

McNeil Laboratories, McNEILAB, Inc., Fort Washington, PA 19034

© McN 1978



Over 20 years of progress in cancer chemotherapy

CYTOXAN®
(CYCLOPHOSPHAMIDE)

a chemotherapeutic agent of ever increasing importance

Since its introduction in 1959 as one of the first potent cytotoxic agents, intensive pharmacological and clinical studies with CYTOXAN have led to broad usefulness in 15 malignancies, with predictable response.

Further, refinements in the careful usage of CYTOXAN have resulted in increased response rates in several neoplasms. For instance, with intermittent dosage schedules of 10 mg/kg/week instead of daily schedules, the response rate in rhabdomyosarcoma increases to over 80%, to about 65% in neuroblastoma, and to about 60% in Ewing sarcoma.[1]

injectable and oral dosage forms

CYTOXAN is available in vials of 100 mg, 200 mg, and 500 mg for injection and in oral tablets of 25 mg and 50 mg.

Chemotherapy with CYTOXAN, as with other drugs used in cancer chemotherapy, is potentially hazardous and fatal complications can occur. It is recommended that it be administered only by physicians aware of the associated risks.

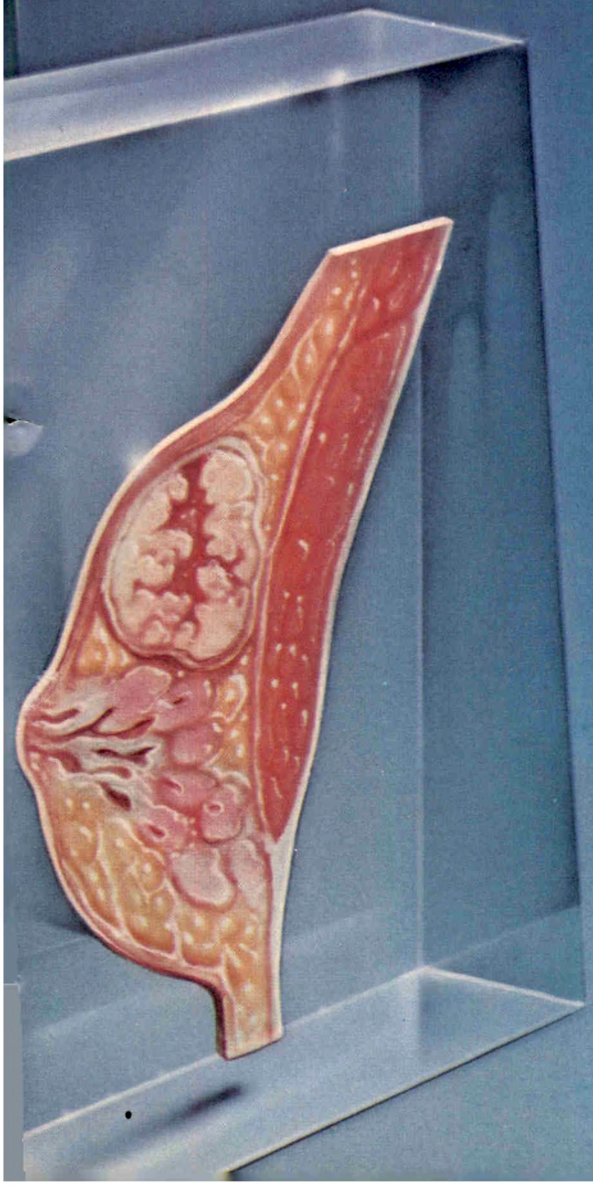
1. Block JB: Drugs for cancer, in Modell W, (ed): *Drugs of Choice 1978-1979.* St Louis, C. V. Mosby Co, 1978, pp 580-608.

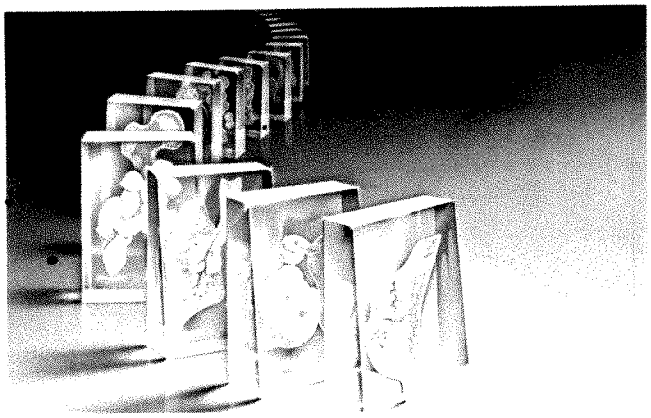
Mead Johnson
PHARMACEUTICAL DIVISION

CYTOXAN®
(CYCLOPHOSPHAMIDE)

adaptable broad spectrum cancer chemotherapy

For prescribing information, please see the following page.





CYTOXAN®
(CYCLOPHOSPHAMIDE)

INDICATIONS

- A. Frequently responsive myeloproliferative and lymphoproliferative disorders:
  - 1 Malignant lymphomas (Stages III and IV, Peter's Staging System).
    - a. Hodgkin's disease
    - b. Follicular lymphoma
    - c Lymphocytic lymphosarcoma.
    - d. Reticulum cell sarcoma.
    - e Lymphoblastic lymphosarcoma.
    - f. Burkitt's lymphoma.
  - 2 Multiple myeloma.
  - 3 Leukemias:
    - a. Chronic lymphocytic leukemia.
    - b Chronic granulocytic leukemia (it is ineffective in acute blastic crises).
    - c Acute myelogenous and monocytic leukemia.
    - d. Acute lymphoblastic (stem-cell) leukemia in children (cyclophosphamide given during remission is effective in prolonging its duration).
  - 4 Mycosis fungoides (advanced disease).
- B Frequently responsive solid malignancies.
  - 1 Neuroblastoma (in patients with disseminated disease).
  - 2 Adenocarcinoma of the ovary.
  - 3 Retinoblastoma.
- C. Infrequently responsive malignancies:
  - 1 Carcinoma of the breast.
  - 2 Malignant neoplasms of the lung.

WARNINGS

Since Cytoxan has been reported to be more toxic in adrenalectomized dogs, adjustment of the doses of both replacement steroids and Cytoxan may be necessary for the adrenalectomized patient.

The rate of metabolism and the leukopenic activity of Cytoxan reportedly are increased by chronic administration of high doses of phenobarbital. The physician should be alert for possible combined drug actions, desirable or undesirable, involving Cytoxan even though Cytoxan has been used successfully concurrently with other drugs, including other cytotoxic drugs.

Cytoxan may interfere with normal wound healing.

Usage in Pregnancy. Cytoxan can be teratogenic or cause fetal resorption in experimental animals. It should not be used in pregnancy, particularly in early pregnancy, unless in the judgment of the physician the potential benefits outweigh the possible risks. Cytoxan is excreted in breast milk and breast-feeding should be terminated prior to institution of Cytoxan therapy.

Patients, male or female, capable of conception ordinarily should be advised of the mutagenic potential of Cytoxan. Adequate methods of contraception appear desirable for such patients receiving Cytoxan

PRECAUTIONS

Cytoxan should be given cautiously to patients with any of the following conditions

1. Leukopenia
2. Thrombocytopenia
3. Tumor cell infiltration of bone marrow
4. Previous X-ray therapy
5. Previous therapy with other cytotoxic agents
6. Impaired hepatic function
7. Impaired renal function

Because Cytoxan may exert a suppressive action on immune mechanisms, the interruption or modification of dosage should be considered for patients who develop bacterial, fungal or viral infections. This is especially true for patients receiving concomitant steroid therapy and perhaps those with a recent history of steroid therapy, since infections in some of these patients have been fatal. Varicella-zoster infections appear to be particularly dangerous under these circumstances.

ADVERSE REACTIONS

Secondary Neoplasia. Secondary malignancies have developed in some patients treated with cyclophosphamide alone or in association with other antineoplastic drugs and/or modalities. These malignancies most frequently have been urinary bladder, myeloproliferative, and lymphoproliferative malignancies. Secondary malignancies most frequently have developed in the cyclophosphamide-treated patients with primary myeloproliferative and lymphoproliferative malignancies and primary nonmalignant diseases in which immune processes are believed to be involved pathologically. In some cases, the secondary malignancy was detected up to several years after cyclophosphamide treatment was discontinued. The secondary urinary bladder malignancies generally have occurred in patients who previously developed hemorrhagic cystitis (see Genitourinary under Adverse Reactions). Although no cause-effect relationship has been established between cyclophosphamide and the development of malignancy in humans, the possibility of secondary malignancy, based on available data, should be considered in any benefit-to-risk assessment for the use of the drug.

Hematopoietic. Leukopenia is an expected effect and ordinarily is used as a guide to therapy. Thrombocytopenia or anemia may occur in a few patients. These effects are almost always reversible when therapy is interrupted

Gastrointestinal. Anorexia, nausea, or vomiting are common and related to dose as well as individual susceptibility. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration and jaundice occurring during therapy.

Genitourinary. Sterile hemorrhagic cystitis can result from the administration of Cytoxan. **This can be severe, even fatal, and is probably due to metabolites in the urine.** Nonhemorrhagic cystitis and/or fibrosis of the bladder also have been reported to result from Cytoxan administration. Atypical epithelial cells may be found in the urinary sediment. **Ample fluid intake and frequent voiding help to prevent the development of cystitis,** but when it occurs it is ordinarily necessary to interrupt Cytoxan therapy. Hematuria usually resolves spontaneously within a few days after Cytoxan therapy is discontinued, but may persist for several months. In severe cases replacement of blood loss may be required. The application of electrocautery to telangiectatic areas of the bladder and diversion of urine flow have been successful methods used in treatment of protracted cases. Cryosurgery has also been used. (See also Secondary Neoplasia under Adverse Reactions.) Nephrotoxicity, including hemorrhage and clot formation in the renal pelvis, have been reported.

Gonadal suppression, resulting in amenorrhea or azoospermia, has been reported in a number of patients treated with cyclophosphamide and appears to be related to dosage and duration of therapy. This side effect, possibly irreversible, should be anticipated in patients treated with Cytoxan. It is not known to what extent Cytoxan may affect prepuberal gonads. Fibrosis of the ovary following Cytoxan therapy has been reported also.

Integument. It is ordinarily advisable to inform patients in advance of possible alopecia, a frequent complication of Cytoxan therapy. Regrowth of hair can be expected although occasionally the new hair may be of a different color or texture. The skin and fingernails may become darker during therapy. Non-specific dermatitis has been reported to occur with Cytoxan.

Pulmonary. Interstitial pulmonary fibrosis has been reported in patients receiving high doses of Cytoxan over a prolonged period.

DOSAGE AND ADMINISTRATION

Chemotherapy with Cytoxan, as with other drugs used in cancer chemotherapy, is potentially hazardous and fatal complications can occur. It is recommended that it be administered only by physicians aware of the associated risks. Therapy may be aimed at either induction or maintenance of remission.

Induction Therapy. The usual initial intravenous loading dose for patients with no hematologic deficiency is 40 – 50 mg/kg. This total initial intravenous loading dose usually is given in divided doses over a period of two to five days.

Patients with any previous treatment that may have compromised the functional capacity of the bone marrow, such as X ray or cytotoxic drugs, and patients with tumor infiltration of the bone marrow may require reduction of the initial loading dose by 1/3 to 1/2.

A marked leukopenia is usually associated with the above doses, but recovery usually begins after 7 – 10 days. The white blood cell count should be monitored closely during induction therapy.

If initial therapy is given orally, a dose of 1 – 5 mg/kg/day can be administered depending on tolerance by the patient.

Maintenance Therapy. It is frequently necessary to maintain chemotherapy in order to suppress or retard neoplastic growth. A variety of schedules has been used:

(1) 1 – 5 mg/kg p.o. daily
(2) 10 – 15 mg/kg i.v. every 7 – 10 days
(3) 3 – 5 mg/kg i.v. twice weekly

Unless the disease is unusually sensitive to Cytoxan, it is advisable to give the largest maintenance dose that can be reasonably tolerated by the patient. The total leukocyte count is a good objective guide for regulating the maintenance dose. Ordinarily a leukopenia of 3000-4000 cells/cu. mm. can be maintained without undue risk of serious infection or other complications.

Preparation and Handling of Solutions. Cytoxan for Injection should be prepared for parenteral use by adding **Sterile Water for Injection, U.S.P.** or **Bacteriostatic Water for Injection, U.S.P. (paraben preserved only)** to the vial and shaking to dissolve. Use 5 ml. for the 100-mg. vial, 10 ml. for the 200-mg. vial, or 25 ml. for the 500-mg. vial. Solutions of Cytoxan for Injection may be injected intravenously, intramuscularly, intraperitoneally or intrapleurally or they may be infused intravenously in Dextrose Injection, U.S.P. (5% dextrose) or Dextrose and Sodium Chloride Injection, U.S.P. (5% dextrose and 0.9% sodium chloride). These solutions should be used within 24 hours if stored at room temperature or within 6 days if stored under refrigeration. Cytoxan for Injection does not contain an antimicrobial agent and **care must be taken to insure the sterility of prepared solutions.**

Extemporaneous liquid preparations of Cytoxan for oral administration may be prepared by dissolving Cytoxan for Injection in Aromatic Elixir, U.S.P. Such preparations should be stored under refrigeration and used within 14 days.

OVERDOSAGE

No specific antidote for Cytoxan is known. Management of overdosage would include general supportive measures to sustain the patient through any period of toxicity that might occur.

HOW SUPPLIED

Cytoxan® (cyclophosphamide) for Injection. With sodium chloride.

NDC 0087-0500-01 100 mg vials, cartons of 12
NDC 0087-0501-01 200 mg vials, cartons of 12
NDC 0087-0502-01 500 mg vials, cartons of 12

Cytoxan® (cyclophosphamide) tablets.

NDC 0087-0503-01	50 mg. bottles of 100
NDC 0087-0503-02	50 mg. bottles of 1000
NDC 0087-0503-03	50 mg. Unit Dose cartons of 100
NDC 0087-0504-01	25 mg. bottles of 100

REFERENCES

References on selected topics and a physician's brochure are available by writing to: Medical Affairs Department, Mead Johnson Pharmaceutical Division, Evansville, Indiana 47721.

Mead Johnson PHARMACEUTICAL DIVISION

© 1979 Mead Johnson & Company • Evansville, Indiana 47721 U.S.A. MJL 9-4441

ANNALS OF SURGERY

Vol. 190 September 1979 No. 3

Presidential Address:

The Unfinished Painting

OLIVER H. BEAHRS, M.D.

From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Dr. Murray, members of the American Surgical Association and guests, to be elected President of the American Surgical Association is the greatest honor that could come to an American surgeon. I am very humble in recognition of this, for there are many of you, members of this great and distinguished Association, who deserve this recognition more than I. In accepting the presidency this year, I do it not only with humility and in great appreciation of the honor you have bestowed upon me, but also in recognition of the great medical institution with which I have been associated for almost 40 years—founded by two brothers, one President of the Association in 1913 and the other President in 1931—and in recognition of the meaning of the clinical practice of surgery. The last is what our profession is all about: educating ourselves and those about us to a high level of knowledge, evaluating the old and seeking out the new so that we can provide the best of our capability to our fellow man—the patient.

Somewhere I have read that if you really want to make a good speech you should say, "to be seen, you must stand up. To be heard, you must speak out. To be appreciated, you must sit down." Possibly I should consider this advice, but I will take the risk and speak for a short while.

During the past year, I have read the correspondence of Dr. William J. Mayo while he was President of the American Surgical Association. I would like to take note of several items. A letter to him from another member of the Association stated, "I guess we should not lug the women along but leave them in Chicago." A happy change has occurred over the years—our ladies are with us now and rightly so, since they contribute so much to us as surgeons and remain tolerant and interested in our "shop talk" during social affairs, meetings and at home, although they might be more interested in other subjects or activities. Their support makes it possible in many respects for members of the Association to hold the positions and the respect within the profession that they do. Our thanks to them.

In another letter by Dr. Will to the President of the American Surgical Association in 1921, he expressed, among others, the thoughts that the American Surgical Association should not be looked upon as a private club.

> It seems to me that the Fellows of each generation are merely trustees, and that any American, without regard to race, creed, or color, who accomplishes the work that entitles him to membership is eligible, and that objections to him on personal grounds should not be tolerated.[12]

He later also stated that he thought it would be wise for the Association to choose for its Fellows more persons in their 30s to stimulate them to do their best.

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

0003-4932/79/0900/0265 $00.95 © Copyright 1979 Mayo Foundation

Certainly this philosophy should continue to hold true today. Membership should be in recognition of past and current achievements and future promise in the fields of patient care, education, research and medical socioeconomics. Our present and recent new member classes reflect this attitude, and we look to these new members for leadership in the field of American Surgery now and in the future in our changing medical and societal environment.

Presidential addresses presented before the Association over the years have included topics of scientific interest, medical education, research, review of the history of the American Surgical Association (founded in 1880) and descriptions of the great men of surgery and their contributions. All are subjects of interest and of value, especially the last, because for us today, as has been so well said before, we see as far as we do because we stand on the shoulders of giants. The groundwork and foundations have been laid for us by our predecessors, and it is our obligation and responsibility to maintain the excellence in our profession for those who follow. Today, rather than cover only a single aspect of what concerns the surgical community today, my remarks will relate to what I regard as an important group of problems—education as it affects patient care, the patient-doctor relationship, residency training, government relations and cost containment and other socioeconomic issues.

In the past, our primary interests have revolved around the art and science of medicine. The socioeconomic issues affecting medicine and health care were only secondarily of interest. Today we are embroiled in controversy regarding the administrative structure of providing health care, cost containment, quality assurance of medical service, liability for unfavorable results, malpractice, recertification, relicensing, medical manpower and its distribution, second opinions and unnecessary surgery.

Eiseman[7] has stated in an editorial, *Surgery's Greatest Challenge*, "A horde of aggressive social planners and economists are rushing to solve our problem for us. Like self-confident politicians dealing with warfare, they consider the problem to be too serious to be left to the generals."

Unfortunately, the profession has not taken a leadership role in these areas, and as a result, government, industry, labor and the public have forced us into a compromising position on many of these issues. We have more often reacted rather than led. We must dream of the future and take the initiative. Government, because of its power and control of funds and with the encouragement of individuals or parties with evangelistic fever, is playing a dominant role in shaping the future. Yet government has met with uniform failure in many, if not most, of the programs it has undertaken, by interfering with the marketplace.

I recall seeing a quotation that has stayed with me because of, I think you will agree, its remarkable relevance to our times. It was from a speech delivered by a statesman to the governing body of his own time and place. He declared that the budget should be balanced, the treasury should be filled, public debt should be reduced, the arrogance of officials should be tempered and assistance to foreign lands should be curtailed lest the state become bankrupt. And he advised that people should be forced to work and not depend on government support. The statesman was Cicero, and he was addressing the Roman senate some 2000 years ago. It is interesting that history does not change, and we do not always learn from the past.

William Simon, in his book, *A Time for Truth*, has pointed out what government today has forgotten:

> In sum, individual liberty *includes* the individual's economic freedom, and the Founding Fathers knew it. They had good reason to leave the productive activities of men as free as possible. Their calculations, like those of Adam Smith, were correct. When men are left free by the state to engage in productive action, guided by self-interest above all, they do create the most efficient and powerful production system that is possible to their society.[17]

It is our responsibility to develop further an efficient and powerful production system—a system of health care delivery that will offer people in our society quality care and good health. Government is already in the act, so we must work with it to create the best system of medical service, protecting, above all else, the patient's welfare.

Rather than dwell on these issues without direction, I would like to center my further comments on an unfinished painting by Brynjalf Stranderes (Fig. 1). Before it could be finished, the artist became ill from a vascular accident and never painted again. In his frustration, he had slashed the picture. For many years it was lost; eventually discovered, it was restored and framed in its unfinished state. It now hangs in the Mayo Foundation House, the former home of Dr. William J. Mayo. A painting of medicine and surgery can never be finished. The future and the art and science of medicine and surgery will always be changing, so that the final touches can never be applied.

So much can be read into this painting—our heritage represented by Dr. William Worrall Mayo and his wife, the present by Drs. Will and Charlie, the future by Drs. Joe and Chuck, teamwork as illustrated by the two

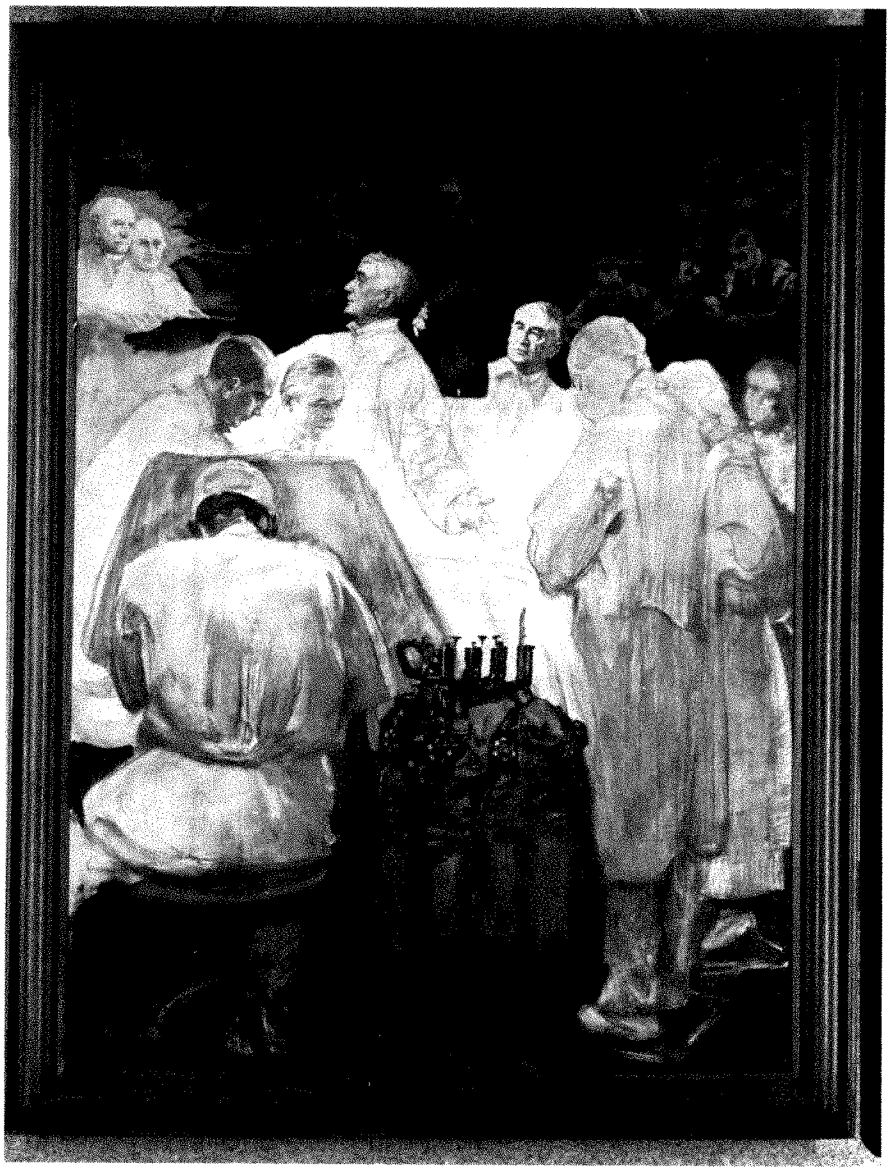


FIG. 1. An unfinished painting of the Mayo Brothers by a well-known Norwegian painter, Brynjulf Stranderes, left incomplete when the painter suffered a cerebrovascular accident. The painting, nevertheless, depicts the field of surgery—heritage, teamwork and the art and the science.

brothers who worked as one along with their associates, surgical nurses and assistants, education by the observers in the gallery and science by the anesthesia equipment in the foreground; and the hand is outstretched to the unseen and never to be forgotten one, the patient. The painting is that of the world of surgery as it should be.

If all of our concerns and questions regarding health matters were always made on the basis of what is best for the patient, the decisions would almost always be right. Unfortunately, as Schlicke[16] has pointed out, "... that suffering human being, the patient, has become the 'consumer,' the dedicated physician who ministers to his ailments the 'provider,' and a respected profession and its allies are referred to as the 'health care industry.' " As physicians, we must be positive in attempting to maintain a more personal relationship and not let a sense of coldness come between doctor and patient, as is implied by these terms. A further drift in that direction will lead to greater breakdowns in the best environment in which to provide health care to the patient, namely, one of mutual respect between the patient and doctor, society and profession. Compromises of ethics or principle should not be accepted if they interfere with what is considered best for the patient.

Throughout the years, Dr. Donald C. Balfour, as surgeon-teacher and as Director of Mayo Graduate School, kept before the minds of the younger physicians at Mayo the principle that preservation of the physician-patient relationship was the highest attainment to which a physician could aspire, and maintaining this would continue to constitute a real contribution to medicine regardless of the form medical practice might take. We should remember this and accept alteration in the form of medical practice only if this principle is maintained.

Considering the patient an inanimate object, a consumer or a financial resource detracts from the relationship and hardly fulfills the requirement of the principle of Fellowship of the American College of Surgeons, which is stated as follows: "Each Fellow must demonstrate professional, moral, and ethical fitness. Surgery is to be practiced with scientific honesty, placing the welfare of patients above all else."[2]

The patient must remain a human being to the surgeon, whose primary concern should be to provide the best of medical care to him. Clinical practice, in addition to providing care, involves education of the patient, one's associates and the public.

As Victor Johnson stated,

> The desire, the need to teach, is as old as the profession of medicine. The Hippocratic oath of antiquity admonishes the physician not only to care well for his patients, but to teach the art and practice of medicine to young aspiring also to become physicians. In no other profession is the urge to teach more compelling than in medicine. In truth, the very word "doctor" means "teacher."[11]

This is well illustrated in our unfinished painting. Medical education has undergone changes over the years. At first, it was strictly a preceptorship and frequently a proprietary arrangement between teacher and student. With the Flexner report,[9] medical education changed and has gradually drifted to a program of graded responsibility and learning as the resident years pass, at times at the expense of the patient. The certifying boards, not always placing the patient first in consideration, too often look at the details of a program—the mechanisms, the administration, the right to anatomic territory or systems, a fixed pattern of training—and not at the end result, that is, at the evaluation of a well-trained surgeon, learned not only in the science of surgery but also in its art on the basis of having seen it applied by the experienced surgeon. It should be recognized that the resident can reach the end point in his training by varied routes and elastic programs. The Flexner report did not rule out preceptorship, but unfortunately many programs have drifted far from it. A residency is an educational program, and how can the student learn better than by close association with an established surgeon—observing his management of surgical problems and participating with him in the surgical procedure, watching mature surgical judgment being used in the care of the patient and at some point in his training finally participating?

Unfortunately, if an educational program does not provide close and careful supervision of the student during his training period by an experienced surgeon, not just the resident a year ahead of him, our obligation to the patient, to all patients, is not being fulfilled.

Loyal Davis, in an editorial, stated,

> Patients have always trusted a person, not a hospital. In spite of society's opulence in this day and age, this fact still remains true. They wish to choose their doctor and have his experience and interest in them as persons and also direct the entire plan of helping them get well. They also wish him to direct investigative studies and the order in which they will be done; choose consultants; and supervise writing orders for their medications. They cannot approve putting the reins of their care in the hands of the house staff. When they learn that interns and residents write orders, plan studies which experience would deem unnecessary, call consultants, and order their discharge from the hospital, they lose confidence and seek medical help elsewhere.
>
> The patient is and should be of primary concern to the physician and surgeon. He is not the jurisdictional right of members of the house staff. . . .[4]

The patient has the right to choose a physician and to expect the best of him, irrespective of that patient's social or economic status. Socialized medicine would take away this right.

With government and other third parties playing such an important role in financing medical care, members of our enlightened society expect to select their physicians and surgeons and to participate in decision-making or at least in selecting an alternative in management. Surgical training environments must accept this change and alter their educational programs accordingly. And this is not all bad, because the patient must come first—he or she deserves an environment, a decision and an action mechanism that offer the best of mature medical and surgical judgments, leading to the best of care. Although some educators might contest this, educational programs would be enhanced by this change.

In a recent visit to a country where private medicine is illegal and an impersonal system is available to all, I found that an estimated 80% of the population seek private care so that they can select their own physicians and the medical service they desire. Even though this is illegal, the law is not enforced, because it is recognized that the population wants more than can be offered by a socialistic system. Although health care is considered by some to be a right, it is and should be a patient's

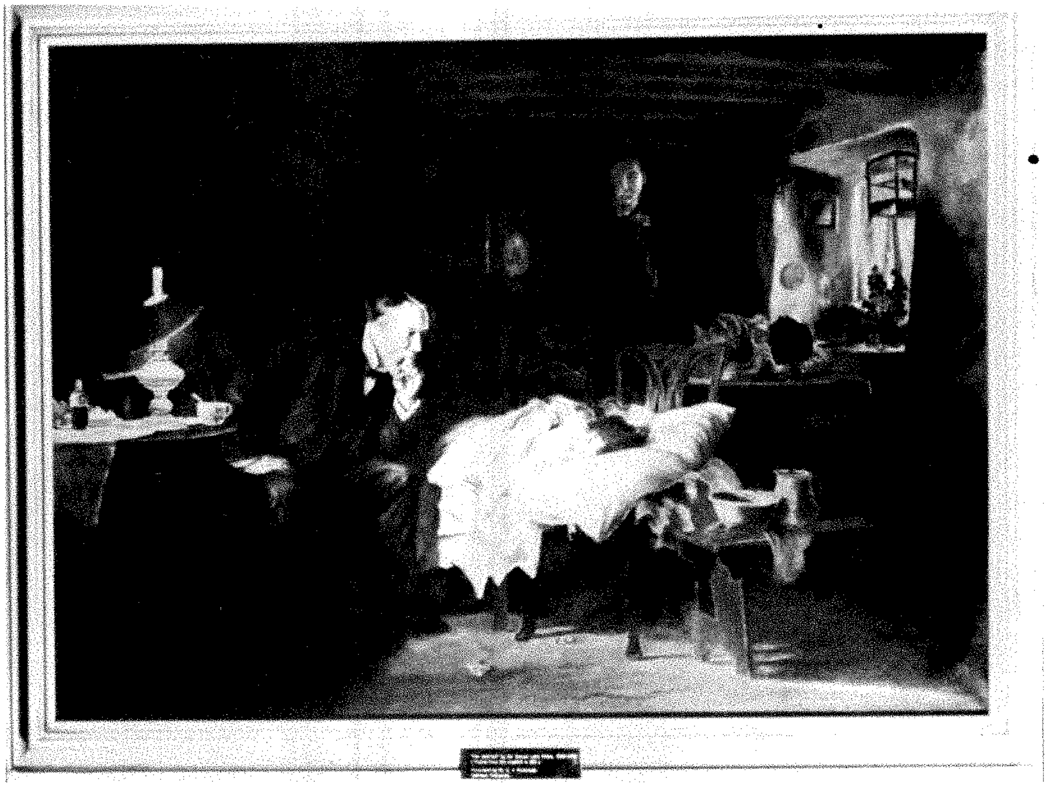


FIG. 2. The painting "The Doctor" by Sir Samuel Luke Fildes. This illustrates so well the art of medicine and surgery—looking at the patient, touching him, contemplating the various factors to be considered in reaching a judgment regarding the management of the clinical problem.

responsibility—the right should be for the patient to expect quality care and to select the environment and physician to provide it.

This does not imply that the resident or student does not participate in the care of the patient, but he or she should do so under the eye of the teacher during the whole of the training program. In this respect, I too would like to cite Henry Brooks Adams, as a predecessor of mine did: "A teacher affects eternity, he can never tell where his influence stops."[1]

The art of medicine is learned by observation—seeing it practiced. It cannot be learned from a textbook or by trial and error in the care of patients. To look at the patient, study his expression, feel his skin and pulse—to touch—will often provide a better evaluation of the patient's condition than will a study of the chart (Fig. 2). The best of patient care, however, is the melding of the art and science of medicine, and through this process proper judgement can be reached.

As Dunphy has said,

> Remember that in surgery, because of the complexities of human biology, decisions must often be made on the basis of probabilities, not certainties, and a life may hang in the balance. Making the correct decision is what is called "judgment"—an amalgam of intelligence, knowledge, experience, and continuous critical analysis of results. Like war it is hard. But it is better than war; it saves lives and binds men and women of good will together in deepest friendship.[5]

As Hall has pointed out in an editorial entitled *The Surgery of Hesitation*, "A surgeon may be endowed with superb qualifications but not be capable of carrying into action many simple operations because of a predisposition to vacillate."[10] The operating room is where the students need to see judgment exercised. The mature surgeon knows, or should know, surgical embryology, anatomy, gross pathology and the biologic behavior of disease. Evaluating the historical, physical and laboratory facts and the findings at the operating table, he should quickly come to a surgical judgment. Sophisticated and costly tests are not always needed.

Once a decision has been made and the correct procedure has been decided upon, the surgeon should be so organized that the operation can be carried out in a stepwise manner with facility and in the shortest period of time consistent with safety. Generally speaking, when this is true, the patient benefits, and this is what surgery is all about. A surgeon might perform a procedure in an hour, and a resident under the preceptorship of a surgeon might do it in two hours, and this is acceptable; but when the same procedure takes four to six hours and without proper supervision, something is obviously

LIBRARY

wrong. Erlik has called this the "surgical disease."[8] It is morally wrong to expose any patient to preventable risks of morbidity and mortality as a result of hesitancy in making judgments or of being unorganized in carrying out a surgical procedure.

Owen Wangensteen has recently proposed a "Teacher's Oath." He noted,

> In recent years complaints from medical students that they rarely see their senior clinical teachers are reechoed frequently in the halls of superior medical schools. The bedside teaching, say the complainants, too often is left to the senior house officers. Like the Holy Ghost, say the grumblers, you can feel his presence, but the senior teacher is rarely in evidence.[18]

Shouldn't the student learn from the giants? And Wangensteen proposes that the teachers take an oath—a commitment to teach.

I hope this has been done by Fellows of the American Surgical Association. In addition, there should be commitment to protect the patient's interest by providing or closely supervising surgical care, which implies a semipreceptor educational environment.

In the past, the surgeon was concerned primarily with the art and science of his profession, but today he must be concerned with another dimension—the cost of providing health care in the best interest of the patient. Proliferation of medical knowledge and research has led to increased capability, which has led to increased utilization, which when compounded with the various factors contributing to inflation has made medical care costs skyrocket. Although the physician personally receives only a small fraction of the health care dollar, he is responsible for utilization of health care capability. Therefore, he does have direct control over the largest proportion of medical costs.

Quality treatment today is not tantamount to unlimited utilization of capability. Unfortunately, the availability of that capability often leads to overutilization, and this is where restraint is necessary if costs are to be controlled. Since quality of care is not evaluable by the third party, MacKenzie[14] suggested to physicians in the United States that they become deeply involved in order to obtain cost control along with high-quality health care. In addition, he said, "Governments will also attempt to arrange rationing unacceptable to individual patients and patients' families by making the decision appear to have been made by health-care providers [physicians]"[14]—another reason why the physician should become deeply involved in deciding the future system of health care delivery.

Without question, we do overutilize our capability and add to costs by not properly using the knowledge known to us in evaluating a clinical situation. We unfortunately practice "defensive medicine," ordering tests and sophisticated examinations because they are available, often in the guise of medical education. Careful evaluation of historical and physical findings in the light of a body of knowledge and known facts will often make further testing in a clinical situation unnecessary. This in part is the art of surgery and the use of judgment based on experience. And this is where the student can learn most in a semipreceptor or a close student–teacher arrangement. Unfortunately, the medical profession has been forced into malpractice considerations, which bypass the use of sound medical judgments. All this adds to cost. The overuse of x-ray, laboratory and specialized services—whether routinely or in the evaluation of a clinical situation—when the needed information can be obtained with available data is inexcusable. Obtaining the whole gamut of "routine" studies as an educational exercise for a student is a questionable procedure indeed. The best educational experience is not only to learn when a study is appropriate but also to know when it is not needed in the evaluation of a clinical situation. Knowledgeable and judicious use of services in providing quality care at a minimum cost is the responsibility of the surgeon, and there is no need to order "the book" to provide the best of care for the patient or for educational purposes. Each test ordered should contribute to, not necessarily corroborate, the diagnosis, or it should provide essential information needed by the surgeon for the proper management of the patient's problem.

Government, industry and labor all agree that health care costs too much. It does, but with conscientious leadership by the medical profession, costs can be controlled. If others are to do it, as has been demonstrated elsewhere, costs will not be controlled, quality of care and accessibility to it will deteriorate, and the patient will suffer. The physician should not let this happen.

The surgeon is entitled to a satisfactory income from his practice to achieve an acceptable standard of living for him and his family and to secure the future beyond the period of active practice. He should not, however, profit beyond that from the care of the sick or the well. Compared with the average college graduate, the physician earned less in 1976 than in 1970. The dollar brought seven times as much in 1954 as it does in 1979, yet costs of medical and surgical fees have increased only 200–400%. Costs of related items and the costs of living have increased considerably in the past 25 years—malpractice insurance 5000%, rent 600%, equipment 2000%, automobiles 500%, groceries 600%, and electrician and plumber fees 500–600%. The surgeon hardly needs to apologize for a reasonable income.[3] Excessive fees and incomes, however, should be condemned.

Dr. Will said,

> . . . monies which should accumulate over and above the amount necessary for a living under circumstances which would give favorable conditions to work and to provide reasonably for our families, would interfere seriously with the object that we had in view [of providing quality treatment to the sick regardless of economic or social position].
>
> Money is so likely to encourage waste of time, changing of objectives in life, living under circumstances which put one out of touch with those who have been life-long friends, who perhaps have been less fortunate. How many families have we seen ruined by money which has taken away from the younger members the desire to labor and achieve and has introduced elements into their lives whereby, instead of being useful citizens, they have become wasteful and sometimes profligate.[13]

And he remembered that any fund that had grown beyond his and his associates' expectations or needs had come from the sick and that ". . . we believed that it ought to return to the sick in the form of advanced medical education, which would develop better trained physicians, and to research to reduce the amount of sickness."

Certainly, if the surgeon held to the goal that he should not profit beyond the needs of his practice, family and the requirements of education and research in the care of the sick, his income from patient care would always be reasonable and he need not apologize for it.

Donald C. Balfour perceived that Dr. William J. Mayo and Dr. Charles H. Mayo made every effort to lessen the emotional, economic and physical burdens of the patient. That is, no patient was ever refused treatment, and all patients were accorded the same treatment regardless of economic or social position.

I do not want to preempt the Committee on Issues of the American Surgical Association, but I would like to identify areas in which the surgeon can be a positive force in cost containment:

1) The surgeon should encourage preoperative evaluation on an ambulatory basis.

2) He should be constantly aware that the simple availability of tests creates demand for their use and encourages repetition, and he should order them or supervise those persons ordering them so that they will be requested only when they are essential to patient care.

3) Educational programs should stress not only the need to order tests and consultation when indicated but also the need to desist from ordering them when they are not necessary or are superfluous. Surgeons, students and house staff should be made cost conscious in all areas of practice.

4) When feasible, surgeons should consider outpatient or office surgery as an alternative to inpatient surgery, if it does not detract from the quality or safety of patient care.

5) As the surgeon makes hospital rounds, he should daily ask the question, "Is continued hospitalization necessary from the medical or surgical standpoint?" Only factors related to the medical or surgical well-being of the patient should be considered. Continued hospitalization should not be considered for the convenience of the patient or family or for other reasons.

6) The surgeon should periodically review total hospital patient charges to keep himself sensitive to costs.

7) Operating room use is costly—the facility should be used efficiently. Operations should be done with dispatch consistent with safety, and effective utilization should be promoted.

8) Surgeons should take time to participate in cost containment, utilization and other committees of the hospital.

9) Surgical fees should be kept at a reasonable level and increased no more than the percentage increase of the gross national product. Surgeons should speak out against unjustified and exorbitant fees and unnecessary consultations.

10) Surgeons individually or through their associations should participate in educational efforts to inform the public regarding surgical care and costs and unreasonable charges.

11) Surgeons or their associations should work closely with third parties to develop insurance programs that include incentives to reduce overutilization of health care services.

12) Surgeons should seek out alternatives to the unstructured fee-for-service compensation system and to determine whether there are more effective alternatives—those that would not alter the doctor-patient relationship and quality of care and still provide the surgeon a reasonable return for his contribution to health care.

If the surgeon considers his patient first—his health and his social and economic well-being—irrespective of the administrative structure of health care delivery, he can take pride in his profession, and the best of men will enter it. The patient will respond with his loyalty and support.

Albert Einstein said,

> How extraordinary is the situation of us mortals! Each of us is here for a brief sojourn; for what purpose he knows not, though he sometimes thinks he senses

> it. But without going deeper than our daily life, it is plain that we exist for our fellow man—in the first place for those upon whose smiles and welfare all our happiness depends, and next for all those unknown to us personally but to whose destinies we are bound by the tie of sympathy. A hundred times every day I remind myself that my inner and outer life depends on the labours of other men, living and dead, and that I must exert myself in order to give in the same measure as I have received and am still receiving.[6]

Finally, I would like to quote from Dr. Will's response when he was honored by the American Surgical Association on his seventieth birthday at the meeting of the Association in 1931, held in San Francisco. The quotes are philosophic but very appropriate and in many respects the embodiment of the ideals of the American Surgical Association.

This, then, is Doctor Will speaking in 1931:[15]

Mr. President and Fellows of the American Surgical Association:

> Your greetings on this seventieth birthday of mine repay me for living long enough to have it. The day in my thirties when I was elected to the American Surgical Association was the proudest day of my professional life. . . . In this connection, I wonder whether it would be not wise for the Association to choose for its Fellows more men in the thirties, with the idea of stimulating them to do their best. . . .
>
> The most important factor in what I may have accomplished . . . [is] my association with my brother. Something more than four years younger, Charlie has stimulated me by precept and example, and our association has been unique not only in the love and confidence we have for each other, but in having made an opportunity for two men to work as one and to share equally such rewards as have come. Even to this day, not only have our fraternal contacts been maintained, but also our habit of having a common pocketbook, in which each has wanted the other to have the greater share. And with due regard to the statement of a truth, my brother, Charles H. Mayo, is not only the best clinical surgeon from the standpoint of the patient that I have ever known, but he has that essential attribute of the true gentleman, consideration for others.
>
> The years have come upon me so easily and so rapidly that I can look back on each and every one of them without regret, and I feel no older now than I did when I came into this Association. As I have watched older men as they have come down the ladder, as down they must come, with younger men passing them, as they must pass to go up, it so often has been an unhappy time for both. The older man is not always able to see the necessity or perhaps the justice of his descent and resents his slipping from the position that he had held, instead of gently and peacefully helping this passing by assisting the younger man. What pleasure and comfort I have had from my hours with younger men! They still have their imagination, their vision; the future is bright before them. Each day as I go through the hospitals surrounded by younger men, they give me of their dreams and I give them of my experience, and I get the better of the exchange. . . .
>
> Before stopping my operative work I visited the clinics of the younger men, and I was convinced that the older man unconsciously loses something of handicraft, something of ready response to operative emergencies. When this became plain to me I was happy to turn, in the interest of the profession that I love so well and of the patients who had been my first thought, from an active surgical career to that of surgical advisor, that I might give to the younger surgeons such of value as I had, and to the patient the benefit of my experience. . . .
>
> As I see the younger men picking up the torch and carrying it on, I realize that scientific truth which I formerly thought of as fixed, as though it could be weighed and measured, is changeable. Add a fact, change the outlook, and you have a new truth. Truth is a constant variable. We seek it, we find it, our viewpoint changes, and the truth changes to meet it.
>
> There are many recompenses in a seventieth birthday. I look through a half-opened door into the future, full of interest, intriguing beyond my power to describe, but with a full understanding that it is for each generation to solve its own problems and that no man has the wisdom to guide or control the next generation. It is a comfortable feeling, to be interested in what is to happen, but in bringing it about to be in no way responsible.

Dr. Mayo expressed faith in the future, in constant search for the truth, in the importance of a close relationship between teacher and student and in a constant concern for the patient.

Although as surgeons we should work with others toward achieving the best administrative system of health care delivery, we must remember above all else our responsibilities as physicians to all patients and to society.

As members of the American Surgical Association we should remain the leaders of surgery, taking unto us the young and being willing to see them surpass us and attain new heights but giving them the best we have, melding together the art and the science of the practice of surgery for the benefit of the patient, adding a new stroke to the painting and realizing that it will be more complete in their day than in ours, but never finished.

Again, to the Fellows of the American Surgical Association, my thanks to you for the greatest honor of my professional career: to have served as your President this year.

References

1. Adams, H. B.: Cited by Sabiston, D. C., Jr.: Presidential Address: Alfred Blalock. Ann. Surg., 188:255, 1978.
2. American College of Surgeons: Statements on Principles.II. Principles of Qualifications for Fellowship. Bull. Am. Coll. Surg., 60:10, 1975.
3. Davis, F. A.: Why I Had to Raise My Fees. Private Practice, p.7, February, 1979.
4. Davis, L.: Why the Declining Census in University Hospitals? (Editorial) Surg. Gynecol. Obstet., 136:785, 1973.
5. Dunphy, J. E.: Reflections. Contemp. Surg., 10:42, 1977.
6. Einstein, A.: The World as I See It. New York, Covici-Friede, p. 237, 1934.
7. Eiseman, B.: Surgery's Greatest Challenge (Editorial). Arch. Surg., 112:1029, 1977.
8. Erlik, D.: Is Technical Dexterity Still Important in Modern Surgery? (Editorial) Isr. J. Med. Sci., 9:3, 1973.
9. Flexner, A.: Medical Education in the United States and Canada: A Report to the Carnegie Foundation for the Advancement of Teaching. Bulletin No. 4. New York, Carnegie Foundation for the Advancement of Teaching, 1910.
10. Hall, D. P.: The Surgery of Hesitation (Editorial). Am. J. Surg., 110:360, 1965.
11. Johnson, V.: Origins and Development of the Mayo Foundation: Presented to Rochester Chamber of Commerce and Service Clubs, Rochester, Minnesota, March 19, 1964.
12. Letter from Dr. W. J. Mayo to Dr. John B. Roberts, President of the American Surgical Association, May 26, 1921.
13. Letter to the University of Minnesota from Dr. William J. Mayo, February 15, 1934.
14. MacKenzie, W. C.: The Canadian Health System: Discontent Among the Ranks. Bull. Am. Coll. Surg., 64:8, 1979.
15. Mayo, W. J.: Seventieth Birthday Anniversary of William J. Mayo. Ann Surg., 94:799, 1931.
16. Schlicke, C. P.: American Surgery's Noblest Experiment. Arch. Surg., 106:379, 1973.
17. Simon, W. E.: A Time for Truth. New York, McGraw-Hill, p. 22, 1978.
18. Wangensteen, O. H.: Teacher's Oath (Letter to the Editor). J. Med. Educ., 53:524, 1978.

Glucose Requirements Following Burn Injury

Parameters of Optimal Glucose Infusion and Possible Hepatic and Respiratory Abnormalities Following Excessive Glucose Intake

JOHN F. BURKE, M.D., ROBERT R. WOLFE, PH.D., CHARLES J. MULLANY, M.D.,
DWIGHT E. MATHEWS, PH.D., DENNIS M. BIER, M.D.

From the Surgical Services of the Massachusetts General Hospital and Shriners Burns Institute, Boston, and the Department of Medicine, Washington University School of Medicine, St. Louis, Missouri

Glucose and leucine metabolism in 18 severely burned patients were studied using the primed constant infusion of U-^{13}C-glucose and 1-^{13}C-leucine, respectively. The leucine data were used to calculate rates of whole-body protein synthesis. In four additional burn patients and seven normal controls, the effects of exogenously infused insulin on the metabolism of infused glucose were evaluated. Also, the effect on leucine metabolism of adding insulin to infused glucose was tested and rates of protein synthesis were calculated. The protein studies were divided into two groups depending on the rate of glucose infusion. Protein synthesis was 4.3 + 0.54 g protein/kg/day during the lower infusion rates (1.4–4.5 mg/kg/min) and 5.17 + 0.19 g protein/kg/day during the higher infusion rates (4.7–9.3 mg/kg/min) (statistically different, $p < 0.05$). However, when the high infusion rate group was divided into two subgroups (high, 4.7–6.8 mg/kg/min, and very high, 7.03–9.31 mg/kg/min), there was no difference in the rate of protein synthesis. When U-^{13}C-glucose was infused during varying rates of unlabeled glucose infusion, we found that the per cent of CO_2 coming from the direct oxidation of glucose rose rapidly at the lower infusion rates but reached a plateau at approximately 55% as the infusion rates exceeded 5 mg/kg/min. Addition of insulin did not affect the rate of glucose oxidation but did seem to exert a stimulatory effect on protein synthesis. It was concluded that there appears to be a maximal rate of glucose infusion, beyond which physiologically significant increases in protein synthesis and direct oxidation of glucose cannot be expected. Furthermore, there appears to be a physiological cost of exceeding the optimal glucose infusion rate, as indicated by increased rates of CO_2 production during infusion as well as large fat deposits in the liver at autopsy in patients infused with large amounts of glucose.

A NEGATIVE NITROGEN BALANCE and hyperglycemia point to the extensive changes in protein and carbohydrate metabolism in response to injury. This reaction, although possibly effective in the short term, requires that a substantial amount of exogenous substrate be given following injury and resuscitation to reverse catabolism. Thus, intravenous delivery of substrate—usually glucose and amino acids—is used extensively to provide energy and protein precursors in an attempt to bring about anabolism. However, the exact amount of each that will provide sufficient energy and protein precursors to ensure an optimal level of protein synthesis over catabolism is an important but unsettled issue. In addition, although the long-term importance of undernutrition is recognized, the consequences of overnutrition (made possible by the ease of central venous delivery of extensive quantities of glucose), particularly the metabolic and respiratory consequences, have not been thoroughly examined.

In order to obtain information concerning the rate of exogenous glucose delivery required to provide optimal protein synthesis over catabolism following injury, as well as obtain information on the possible consequences of glucose overload, we have studied the effects of graded increases in intravenous glucose delivery with a fixed amino acid delivery on seriously burned patients in the acute phase of their injury following resuscitation and before complete wound closure. The techniques used gave kinetic information concerning whole body glucose and leucine metabolism. From these data rates of protein synthesis in relation to nitrogen balance are calculated. These studies addressed the following problems: 1) the effect of increasing rates of delivery of exogenous glucose on energy production from glucose as monitored by the proportion of total CO_2 excretion coming directly from glucose; 2) the effect of increasing rates of exogenous delivery of glucose on the rate of protein synthesis; 3) the effect on protein synthesis

---

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

Reprint requests: John F. Burke, M.D., Massachusetts General Hospital Department of Surgery, Boston, Massachusetts.

Supported by NIH Grant GM 21700.

0003-4932/79/0900/0274 $01.10 © J. B. Lippincott Company

brought about by the addition of sufficient exogenous insulin to return the blood glucose toward a normal range during glucose infusion; and 4) to explore the metabolic and respiratory consequences of providing glucose at rates well above the level of energy requirements over long periods of time.

Materials and Methods

Patients and Study Designs

These studies were carried out in burned patients at the Massachusetts General Hospital and Shriners Burns Institute and in normal volunteers. The studies themselves are divided into studies of glucose metabolism and leucine metabolism, including calculated rates of protein synthesis, the effect of exogenous insulin infusions of glucose oxidation and protein synthesis and the respiratory and hepatic effects of providing intravenous glucose at a rate above the level of energy requirement.

Glucose Kinetics and Rate of Oxidation

Twenty-seven studies were carried out in nine burned patients whose ages ranged from 16 to 80 years, average 43 years, and whose burn size averaged 31% body surface area (BSA), ranging from 20 to 61% BSA. Glucose kinetics were studied using the primed constant infusion of trace amounts of sterile, pyrogen-free U-^{13}C-glucose. The isotope infusion rate was approximately 0.0018 mg/kg/min, and the prime-to-infusion ratio was 80:1. All isotope infusions were delivered with a Harvard infusion pump at 0.191 ml/min. All measurements were made during the quasi-equilibrium of tracer enrichment in the plasma (between 9 and 120 min following prime and onset of infusion).

The determination of oxidation of glucose requires the determination of the quasi-equilibrium value for the per cent enrichment of CO_2 in the expired air. In humans, this necessitates a constant infusion of tracer for many hours. In order to complete each study period in two hours, we applied existing tracer theory to priming the bicarbonate pool, thereby achieving equilibrium within this pool within 90 min. We have recently described the theory and validation of this technique.[2] For the U-^{13}C-glucose and ^{13}C-leucine studies we administered approximately 400 μmol of $NaH^{13}CO_3$ at the start of the experiment in order to prime the bicarbonate pool. In all studies a plateau in CO_2 enrichment in expired air was achieved in 90 min. Measurements were made between 90 and 120 min.

In all glucose kinetic and oxidation studies, the subject also received a constant infusion (via Harvard pump at 1.91 ml/min) of unlabeled glucose together with a constant amino acid mixture (Freamine II®). The amount of glucose given changed in a stepwise way with use of a low (1.4–4.5 mg/kg/min), a high (4.7–6.8 mg/kg/min) and a very high (7–9.3 mg/kg/min) glucose infusion rate. The glucose steps were varied at random in order to avoid systematic error, and although the patient had been receiving the approximate level of glucose to be studied for 24 hours, the exact rate of infusion was begun at least 12 hours before the sampling period. During the entire period of studies for each patient, he/she received a constant amino acid infusion (Freamine II®) which delivered the equivalent of 1.33 g protein/kg/day. As far as possible, each patient was studied at each glucose infusion level on successive days to insure as constant a clinical state as possible.

Leucine Kinetics—Protein Synthesis

Forty-seven studies were carried out in nine burned patients whose average age was 28 years (range, 8–72 years) and whose mean burn size was 41% (8–85%) BSA. Leucine kinetics and oxidation were determined using the primed constant infusion of sterile pyrogen-free 1-^{13}C-leucine in trace amounts. The isotope infusion rate was approximately 0.0094 mg/kg/min and the prime-to-infusion ratio was 100:1. All isotope infusions were delivered with a Harvard infusion pump at 0.191 ml/min. All measurements were made during the quasi-equilibrium of ^{13}C-leucine enrichment in the plasma and $^{13}CO_2$ in the expired air achieved between 90 and 150 min following leucine and bicarbonate prime and onset of trace infusion (please see section on glucose kinetics for details of bicarbonate prime). Protein synthesis was calculated from the leucine kinetics and oxidation (see Calculations).

In determining leucine turnover, each subject was studied at least three times at randomly varied glucose infusion rates using the same steps in glucose infusion used to study glucose kinetics, so that the influence of different infusion rates of glucose on leucine turnover and protein synthesis could be determined. The unlabeled glucose and amino acid mixtures (Freamine II) solutions were infused using a Harvard pump at 1.91 ml/min. The unlabeled glucose and amino acid solutions were infused in exactly the same manner as in the glucose kinetic studies. The amino acid mixture was delivered at approximately the equivalent of 1.33 g protein/kg/day over the entire period covered by the studies. Glucose infusion rates were varied randomly for each study using the same steps as in the glucose kinetic studies (low, high and very high). The studies were repeated three to six times in each patient at random levels of glucose intake on successive days as far as clinically possible. The exact glucose and amino acid delivery rate was established at least 12 hours prior to measurement.

Exogenous Insulin Effects on Glucose Oxidation and Protein Synthesis

The effect of added insulin on glucose oxidation was tested in five burned patients (burn size 30–85% BSA) and on protein synthesis in three burned patients (burn size 30–85% BSA). The glucose kinetic and oxidation studies and protein synthesis in studies were done exactly as described above, except a level of unlabeled glucose infusion was chosen for each patient to give moderate hyperglycemia, and a study was done with infused insulin and another was done without on successive days. The studies with and without insulin were alternated.

Autopsy Studies

All of the patients (nine) who died at the Shriners Burns Institute between 1974 and 1978 and who died more than 30 days after injury were evaluated. All had autopsies, and the liver weight, presence of fatty infiltrations of the liver, as well as glucose intake over the 3 weeks before death were evaluated.

Collection of Expired Air: Measurement of Gas Exchange

Oxygen consumption (V_{O_2}) and CO_2 production (V_{CO_2}) were determined in all subjects three times during each study period. Expired air was collected over 6-min intervals in Douglas bags with the use of a two-way Rudolph valve. The O_2 and CO_2 concentration of the expired gas was measured on a Perkin Elmer Model 1100 Medical Gas Analyzer, and the total volume of expired air was measured with use of a Gasometer (Warren E. Collins Co., Braintree, Mass.). Respiratory quotient (RQ) was calculated in the conventional manner.

In order to analyze the enrichment of carbon in expired CO_2, expired air was collected in 3-liter anesthesia bags. The collected air was then bubbled through 0.1 NaOH to absorb the expired CO_2, and the ^{13}C atoms per cent excess in the trapped CO_2 was determined with use of a Nuclide Model 3-60-RMS dual inlet, dual collector, isotope-ratio mass spectrometer and corrected for the background value of ^{13}C in a CO_2 sample collected prior to tracer infusion. From 90 to 150 min after commencement of the study, five collections of expired CO_2 were made for such isotopic analysis.

Blood Sampling

When either U-^{13}C-glucose or l-^{13}C-leucine was infused, a 5-cc blood sample was drawn before the commencement of the study in order to measure the naturally occurring background enrichment of either glucose or leucine in the blood. Subsequent blood samples (5 cc) were then drawn at 90–120 or 150 min into sterile, heparinized syringes. These blood samples coincided exactly with the obtaining of a matched expired air sample for determination of $^{13}CO_2$ enrichment.

Analytical Procedures

Blood samples were kept on ice until centrifuged at 4° to separate the plasma.[15] A duplicate determination of glucose concentration was made on all plasma samples with a glucose AutoAnalyzer® (Beckman, Inc., Fullerton, Calif.).

U-^{13}C-glucose Analysis

When U-^{13}C-glucose was infused the analysis of glucose for its isotopic enrichment (^{13}C) first involved the removal of labeled products of glucose metabolism, such as lactate. The extraction was performed by first precipitating the plasma proteins and passing the supernatant sequentially through anion (Dowex AGi-X8) and cation (Dowex AG50W-X8) exchange columns. The eluate was combusted in a vacuum oven at 1000° and the resulting CO_2 was analyzed for per cent enrichment of carbon on the isotope-ratio mass spectrometer. We have validated this technique of measuring rate of appearance of glucose into the plasma in dogs.[1] In all studies the exact concentration in the unlabeled glucose infusion was determined by diluting the infusate and measuring the glucose concentration on the Beckman glucose analyzer.

l-^{13}C-Leucine Analysis

Each plasma sample was analyzed for l-^{13}C-leucine enrichments, expressed as molecules per cent excess. The enrichments in plasma are determined by combined gas chromatograph-mass spectrometry (GCMS) with selected ion monitoring on one of two systems: a PDP-12 computer-controlled ion monitor on a LKB-900 GC-MS or a voltage sweeping circuit designed for an AEI MS 12 GC-MS.[8,9] With each system, stable isotopic enrichment of glucose or alanine within the range of 0.2–10% can be measured with a coefficient of variation less than 5% of the observed ratio.[5] Isotopic enrichment values for leucine are determined using the *N*-acetyl, *n*-propyl ester (NAP) derivative and represent the mean of duplicate determinations. The ^{13}C enrichments of leucine have been measured in the range of 0.9–2.5 molecules per cent excess, with a coefficient of variation less than 5% of the observed ratio.[12]

The leucine content of both the combined glucose and Freamine II infusate and of the $l\text{-}^{13}C$-leucine infusate was measured on a Beckman 121 Automatic Amino Acid Analyzer.

Plasma Insulin

Plasma insulin was determined by the radioimmunoassay method described by Albano *et al.*[3] utilizing insulin-binding reagent (Wellcome Research Laboratories, Beckman, England) and a human insulin standard (Eli Lilly and Co., Indianapolis, Ind.).

Estimated Nitrogen Balance

During the entire study period complete 24 hour food intake records and urine output collections were made. Because almost all nutrition was given intravenously, feces were scant during the study period and were not collected. Urine was analyzed for creatinine, urea and total nitrogen. A careful intake record was made of all oral and intravenously delivered substrate, including blood, plasma and albumin solutions. The nitrogen content of intake was determined on a 24 hour basis. Nitrogen balance was estimated by subtracting output from intake. All values are expressed as protein equivalent/kg/day. Measurements of urinary creatinines were used to help judge the completeness of 24 hour urine collections. Wound nitrogen loss was not accounted for.

Calculations

Glucose turnover. For the calculation of rate of production of glucose the equation derived from Steele was used.[16] In a steady state the rate of appearance of glucose into the plasma equals its rate of disappearance (or uptake). All our calculations were made at an isotopic steady state.

$$Ra_{gl} = \frac{F(\text{mg/kg/min})}{\%\ \text{enrichment of plasma glucose}}$$

where Ra_{gl} = rate of glucose production (mg/kg/min), F = constant isotopic infusion rate of ^{13}C-glucose (mg/kg/min).

Leucine turnover. Because the leucine infusate contributes 1.5% of the total leucine flux, a correction needs to be made for the contribution that the infusate makes to the total flux. The leucine turnover (or rate of appearance into the plasma) (Ra_{leuc}) was therefore calculated by the following equation:[14]

$$Ra_{leuc} = \left(\frac{\%\ \text{enrichment of the infusate}}{\%\ \text{enrichment of plasma leucine}} - 1\right) \times F$$

where F = rate of isotopic infusion of $l\text{-}^{13}C$-leucine (μmol/kg/min).

Oxidation. The per cent of CO_2 from glucose and the rate of glucose oxidation were calculated by the following equations:[10]

$$\%\ CO_2 \text{ due to glucose oxidation} = \frac{\%\ \text{enrichment of } CO_2/0.81}{\%\ \text{enrichment of plasma glucose}}$$

Glucose oxidation (mg/kg/min) = (% CO_2 due to glucose oxidation × V_{CO_2} × 0.18)/6 where V_{CO_2} is the rate of carbon dioxide production (μmol/kg/min),

$$\text{Leucine oxidation} = \frac{\%\ \text{enrichment of } CO_2}{\%\ \text{enrichment of plasma leucine}} \times \frac{V_{CO_2}}{0.81}$$

Two equations involve division by 0.81 to account for labeled CO_2 retained in the body as determined by $NaH^{13}CO_3$ infusions into burned patients.[2] When determining glucose oxidation, since oxidation of 1 mol of labeled glucose gives rise to 6 mol of labeled CO_2, the right side of the equation is also divided by 6. The figure is multiplied by 0.18 to convert the units to mg/kg/min.

The per cent of the uptake oxidized was determined by dividing the oxidation rate by the total production rate.

Protein synthesis. The model for calculation of protein synthesis is based on the model proposed by Golden and Waterlow.[7] This model assumes that the $l\text{-}^{13}C$ of leucine is either oxidized or incorporated into protein. Thus, by measuring leucine uptake (from kinetic data) and leucine oxidization, protein synthesis can be indirectly calculated.

The rate of appearance of leucine (Ra_{leuc}) into the amino acid or metabolic pool is described by the following equation: $Ra_{leuc} = \dot{I} + \dot{B}$, where $\dot{I}$ is the rate of intake of leucine and $\dot{B}$ is the rate at which leucine appears in the metabolic pool from protein breakdown. The rate of leucine uptake (Rd_{leuc}) is $Rd_{leuc} = \dot{S} + \dot{E} + \dot{M}$. When the plasma concentration of leucine is constant (as in our experiment), $Ra_{leuc} = Rd_{leuc}$, and thus $Ra_{leuc} = \dot{I} + \dot{B} = \dot{S} + \dot{E} + \dot{M}$. $\dot{S}$ is the rate at which leucine is taken up for protein synthesis, $\dot{E}$ is the rate of leucine oxidation and $\dot{M}$ is the rate of metabolism of leucine in other pathways. Assuming $\dot{M}$ is zero, then $\dot{S} = Ra_{leuc} - \dot{E}$.

Hence the rate of protein synthesis is determined by calculating the total turnover of leucine and then subtracting the oxidation rate from the total turnover. This value ($\dot{S}$) gives the rate at which leucine is being directed toward protein synthesis. Since it has been estimated

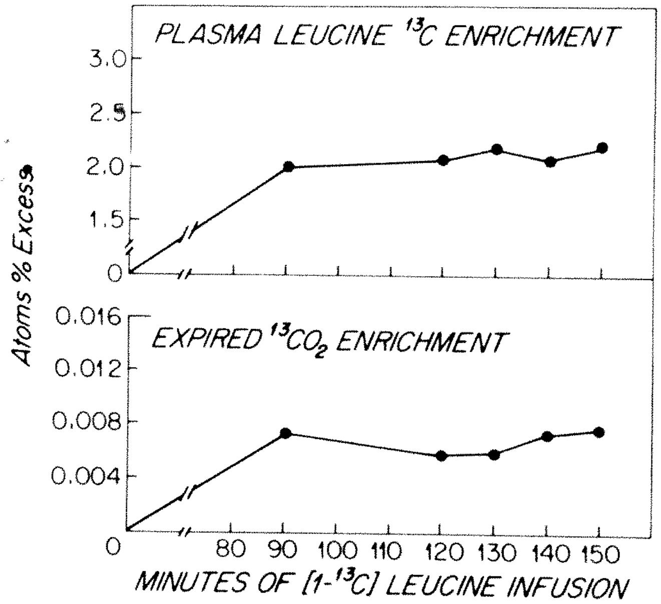


FIG. 1. A representative example of ^{13}C enrichment of plasma leucine and expired CO_2 at 90 min after initiation of primed constant l-^{13}C Leucine infusion.

that total body protein is made up of 8% leucine, then the protein synthesis rate can be calculated from the following equation:

Protein synthesis (g/kg day)

$$= S\ (\mu\text{mol/kg/min}) \times \frac{131.2}{0.08 \times 10^6} \times \frac{24\ \text{hr} \times 60\ \text{min}}{1}$$

Statistics

All values are expressed as means plus or minus the standard error of the means. Curve fitting was carried out using the statistical program available for the Texas Instrument SR-60A computer. Comparisons between two groups of values are made using the Student's t-test.

Results

Nitrogen Balance

All patients were in positive nitrogen balance during the study period, ranging from 7.4 to 0.2 g protein/kg/day, with a mean of 1.7 ± g protein/kg/day, save one who had a negative nitrogen balance of 1 g protein/kg/day on 1 day, although this patient's nitrogen balance was positive for 2 days before and for the remainder of the study period of 7 days. Nitrogen balance remains positive even if the estimated nitrogen loss via the wound is included.[11] The mean nitrogen intake of all patients was 2.75 ± 0.35 g protein/kg/day, and the mean excretion was 1.36 ± 0.11 g protein/kg/day.

Whole Body Leucine Flux and Protein Synthesis

In all subjects an apparent plateau in plasma l-^{13}C-leucine enrichment (atoms per cent excess) had been reached by 90 min after prime and onset of infusion (*e.g.*, Figure 1). Estimation of whole body leucine rate of appearance (Ra) in μmol/kg/min are shown in Table 1. These studies are divided into two groups, depending on the rate of intravenous infusion of glucose in mg/kg/min. Patients studied while receiving the lower levels of glucose had a small change in the total amount of glucose appearing in the plasma (exogenous infusion and endogenous production of glucose), because the amount of glucose given intravenously tended to be balanced by a similar reduction in rate of gluconeogenesis. In the patients receiving higher exogenous glucose levels, the glucose was delivered in excess of the rate of endogenous gluconeogenesis, so that even with suppression of gluconeogenesis the rate of delivery of exogenous glucose caused a marked increase in the total delivery of glucose into the plasma. The rate of appearance of leucine in Group 1 (1.4–4.5 mg/kg/min glucose) and Group 2 (2.7–9.3 mg/kg/min) was similar (3.42 ± 0.17 μmol/kg/min and 3.25 ± 0.15 μmol/kg/min ($p > 0.05$). Despite the lack of difference in the rate of appearance of leucine, the rate of leucine oxidation was lower in Group 2, so that the calculated rate of protein synthesis was higher in Group 2

TABLE 1. *Whole-Body Leucine Rate of Appearance and Protein Synthesis as a Function of Varying Glucose Infusion Rates*

IV Glucose Infusion Rate (mg/kg/min)	Whole Body Leucine Rate of Appearance ("Flux")* (μmol/kg/min)		Whole Body Protein Synthesis† (gm protein/kg/day)	
Group 1: 1.4–4.5	3.55	X̄ = 3.42 ± 0.17	4.31	X̄ = 4.3 ± 0.54
	2.56		3.79	
	3.37		5.84	
	3.18		5.87	
	3.60		5.04	
	4.51		3.96	
	3.30		1.34	
	3.28			
Group 2: 4.7–9.3				
Group 2a, 4.7–6.8	2.77	X̄ = 3.12 ± 0.14	5.44	X̄ = 5.2 ± 0.28
	3.10		5.11	
	3.18		5.21	
	3.11		4.69	
	2.58		5.14	
	3.46		6.20	
	3.29		4.71	
	2.60		3.72	
	4.02		6.90	
Group 2b, 7.03–9.31	2.89	X̄ = 3.47 ± 0.38	4.76	X̄ = 5.05 ± 0.183
	4.00		4.61	
	2.59		5.04	
	2.90		5.80	
	3.01		5.07	
	X̄ = 3.25 ± 0.15 equals mean for combined groups 2a and b		X̄ = 5.17 ± 0.19 equals mean for combined Groups 2a and b	

* Leucine flux $p > 0.05$ for all groups.

† Protein synthesis: Group 1 vs. Group 2, $p < 0.05$; Group 2a vs. Group 2b, $p > 0.05$.

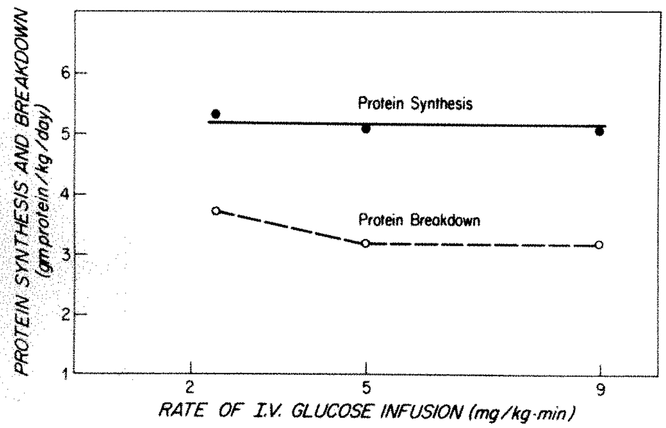


FIG. 2. Rates of protein synthesis and breakdown in an 8-year-old boy with 65% BSA burn during three rates of glucose infusion (2, 5 and 9 mg/kg/min).

(Table 1). The mean rate of protein synthesis in the lower glucose group was 4.3 ± 0.54 g protein/kg/day and for the higher group, 5.17 ± 0.19 g protein/kg/day ($p < 0.05$). However, when the group receiving a higher glucose infusion was broken down into two subgroups (high, 4.7–6.8 mg/kg/min, and very high, 7.03–9.31 mg/kg/min), there was no difference in the rate of protein synthesis in patients receiving high or very high glucose infusion rates. The mean synthesis rate for patients in the high group was 5.2 ± 0.28 and for the very high, 5.05 ± 0.19 g protein/kg/day ($p > 0.05$). All patients in all groups received nitrogen in the form of intravenous amino acids at the rate of 1.33 g protein/kg/day during the study period.

Figure 2 demonstrates the relationships in an 8-year-old patient who had suffered a 65% body surface burn. In addition, for this patient the rate of protein breakdown is also given. Studies were carried out on 3 successive days in the recovery phase following injury. On the three levels of intravenous glucose provided, the synthesis rate was unchanged. The protein catabolic rate, however, decreased between a glucose intake of 2.32 and 5.03 mg/kg/min. There was no further drop in catabolic rate when the glucose intake was increased to 9.31 mg/kg/min. Exogenous leucine intake on these 3 days was identical at 1.21 μmol/kg/min.

The Effect of Exogenous Insulin on Protein Synthesis

The effect of exogenous insulin on whole body leucine rate of appearance and protein synthesis in the young adults studied is demonstrated in Table 2. The patients studied received glucose infusions at a rate which created moderate hyperglycemia. On the day of insulin infusion, the insulin was infused at a rate sufficient to bring the blood sugar toward normal. The mean leucine rate of appearance was 3.10 ± 0.23 μmol/kg/min without insulin and with insulin was 3.20 ± 0.23 μmol/kg/min ($p > 0.05$). However, there was an increase in protein synthesis with insulin. The mean for protein synthesis without insulin was 4.23 ± 0.23 g/kg/day and with insulin was 5.68 ± 0.49 g/kg/day ($p > 0.05$). Although there is an increase in the protein synthesis rate measured, this change is not significant. An additional study was done in an elderly patient who did not fit the pattern seen in the young patients. Because of the known changes in glucose metabolism and insulin sensitivity seen with age[4] and the insufficient number of studies, these data are not included.

Changes in CO_2 from Glucose with Increases in Intravenous Glucose Infusion Rate

The change in the proportion of excreted CO_2 directly derived from glucose oxidation, which results

TABLE 2. *Effect of Insulin Infusion on Rate of Protein Synthesis*

Study	Leucine Flux (μmol/kg/min)	Protein Synthesis (g/kg/day)	Rate of Glucose Infusion (mg/kg/min)	Blood Glucose During Study (mg/dl)	Serum Insulin During Study
Patient #1					
No insulin	3.55	4.31	4.76	127	61.5
Insulin	3.85	6.90	4.96	144	72
Patient #2					
No insulin	3.29	4.71	5.22	186	74
Insulin	2.99	5.14	5.16	180	69
Patient #3					
No insulin	2.60	3.72	6.31	139	65
Insulin	3.01	5.02	7.03	126	75
Means					
No insulin	3.15 ± 0.23	4.25 ± 0.23	5.99 ± 0.32		
Insulin	3.28 ± 0.23	5.69 ± 0.50	6.31 ± 0.47		
	$p > 0.05$	$p > 0.05$			

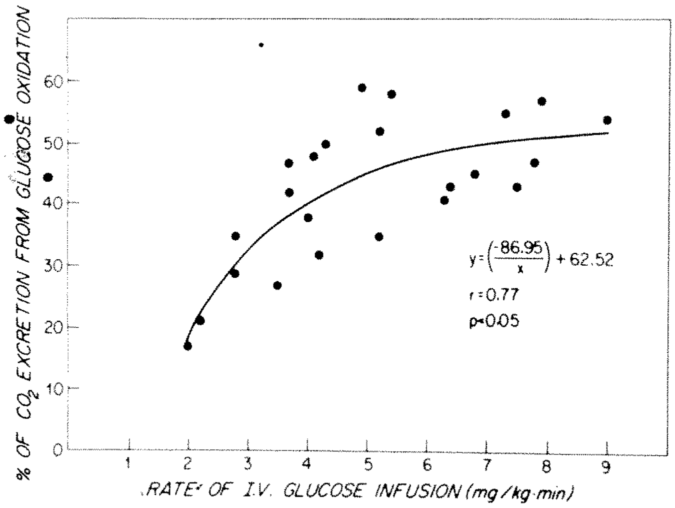


FIG. 3. Correlation between per cent CO_2 production from glucose oxidation and rate of intravenous glucose infusion (mg/kg/min). At infusion rates of less than 2 mg/kg/min the curve would be expected to plateau at about 18%.[18]

from graded increases in the rate of intravenous glucose infusion, is demonstrated in Figure 3. The proportion of CO_2 derived from glucose rises rapidly at low glucose infusion levels and levels off at the higher levels in a statistically significant manner, $R = 0.77$ ($p < 0.05$). At the low levels of glucose infusion the estimated rate of increase in direct glucose oxidation is greater than 10% for each 1 mg/kg/min increase of glucose infusion, while at the high levels there is only about a 2% increase for each 1 mg/kg/min infusion. As a result, there is little increase in direct glucose oxidation from increases in glucose infusion above about 5 mg/kg/min in the patients studied.

The Effect of Exogenous Insulin on the Proportion of CO_2 Derived from Glucose

The effect of intravenously delivered insulin on the rate of glucose oxidation was studied by examining the proportion of the total CO_2 excreted that was directly derived from glucose in both normal volunteers and seriously burned patients. Table 3 demonstrates these findings. In the normal volunteers the addition of insulin to a glucose infusion which had produced moderate hyperglycemia reduced the blood sugar to normal but did not increase glucose oxidation as assessed by the proportion of the total CO_2 from glucose. The mean per cent CO_2 from glucose was 40 ± 2.42 without glucose and 39.4 ± 4.84 with insulin infusion ($p > 0.05$). This was also true in the seriously burned patients studied. In these patients the addition of insulin to the glucose infusion was sufficient to lower the blood sugar concentration but did not increase the rate of glucose oxidation. In the burned patients with a glucose infusion alone the per cent CO_2 from glucose was 47.8 ± 5.2. When a glucose plus insulin infusion was given, the mean per cent CO_2 from glucose was 42.9 ± 2.4 ($p > 0.15$).

Respiratory Quotient as Related to Rate of Glucose Infusion

The relationship of respiratory quotient (RQ) to rate of glucose infusion is demonstrated in Figure 4. The RQ slowly increases as the rate of glucose infusion increases to an RQ of about 1, due to a slow increase in CO_2 production as the level of intravenous glucose delivered increases. However, beyond an RQ of 1, a relatively small increase in the intravenous glucose delivery rate creates a marked increase in RQ and a marked increase in CO_2 production in relation to oxygen consumption. As a result, there is a considerable increase in the volume of CO_2 that the respiratory system is required to excrete.

Fatty Infiltration of the Liver and Very High Glucose Infusion Rates

Between 1974 and 1978 there were nine patients who died more than 1 month following injury who were treated at the Shriners Burns Institute. All patients had an autopsy examination, and all had received glucose infusions in the form of various volumes of Hypercal (glucose + Freamine II) for 3 weeks or more immediately before death. These patients are described

TABLE 3. *The Effect of Added Insulin on CO_2 Production from Glucose*

Means	Rate of IV Glucose (mg/kg/min)	Glucose Oxidation (mg/kg/min)	Per Cent Uptake Oxidized	Per Cent CO_2 from Glucose	Plasma Glucose at Time of Study	Plasma Insulin During Study
7 Healthy volunteers						
No insulin	3.91 ± 0.14	1.49 ± 0.08	32.5 ± 4.31	40.0 ± 2.42	150 ± 6.41	38.1 ± 6.5
Insulin	3.96 ± 0.08	1.47 ± 0.11	33.7 ± 3.82	39.4 ± 4.84	86 ± 2.32	63.2 ± 12.3
5 Burned patients						
No insulin	6.88 ± 0.72	3.89 ± 0.87	53.6 ± 12.8	47.8 ± 5.2	192 ± 37	67 ± 30
Insulin	6.21 ± 0.57	2.95 ± 0.48	51.6 ± 8.0	42.9 ± 2.4	137 ± 26	121 ± 29

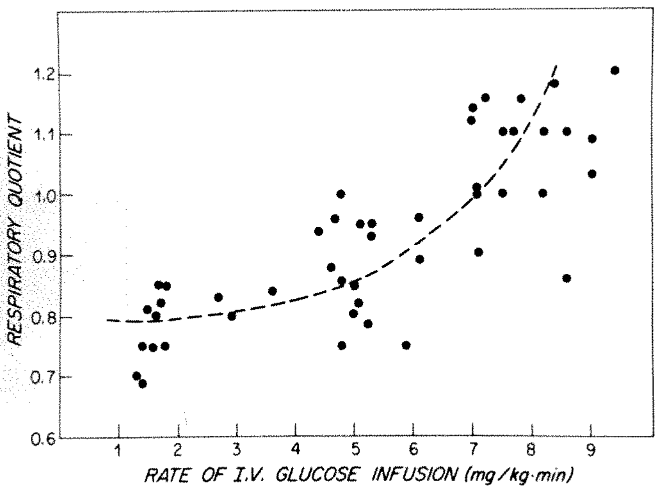


FIG. 4. Respiratory quotient as a function of glucose infusion rate (mg/kg/min) in 47 observations on 18 severely burned patients. The *dotted line* is fitted by eye.

in Table 4. Their average age was seven years, with a range from ten months to 14 years. There were four boys and four girls, and their average burn size was 66% BSA, ranging from 39–86%. No autopsy note was made of muscle wasting in any patient. The rate of glucose infusion for these patients averaged 13.7 mg/kg/min, ranging from 9.3–17 mg/kg/min. At autopsy all showed fatty infiltration of the liver, and their liver weights averaged 273% above normal, with a range of 164–440% above normal.

Discussion

Although the complex metabolic reactions to trauma are not accurately understood, the broad nature of the response with its negative nitrogen balance and the at least partial reversibility of this nitrogen loss with glucose administration have led to treatment regimens which have greatly improved the patient's metabolic state following injury. There is clear evidence that treatment improves nitrogen balance[17] and increases rates of protein synthesis.[11] This success has led to the use of extensive intravenous delivery of amino acids, fat and especially glucose without the establishment of an exact end point. Although the minimum level of glucose delivery required to substantially spare protein was established by Gamble[6] at about 100 g/day (approximately 1 mg/kg/min) in fasting man, there is limited information on the maximum level beyond which further increases in glucose administration would not produce physiological cost-effective increments of energy production and protein sparing in burned patients. The studies reported here provide evidence that there is a maximum physiological cost-effective rate of glucose administration in severely burned patients who were not starving or in the depleted state at the time of injury and whose protein intake was fixed following injury at approximately 1.33 g protein/kg/day. It is probable that patients who are severely depleted or starving would demonstrate a maximum effective rate of glucose administration at a different level. It is also possible that the optimal level of glucose intake identified in this study would shift if a higher or lower level of amino acid intake were used.

The data presented here strongly support the concept that there is a maximum level of glucose intake in relation to energy production and protein synthesis when viewed from the concept of physiological cost effectiveness. The rapid rise in CO_2 produced directly from the glucose at low rates of glucose infusion and the leveling off of glucose oxidation at high rates support this idea. It is of interest to note that even at the highest rate of glucose delivery the per cent of CO_2 derived directly from glucose continues to increase slowly. However, at the highest rates of glucose infusion studied, only approximately 40% of the glucose administered was oxidized, leaving 60% of the administered glucose to be handled via other metabolic pathways. Although we have no direct evidence, we believe that it is probable that the metabolic fate of this unoxidized glucose in this circumstance (*i.e.*, nonstarving or depleted patients receiving very high

TABLE 4. *Autopsy Findings of Patients Treated with Very High Glucose Infections*

Patient	Sex	Age	Per Cent BSA Burned	Muscle Atrophy	Hypercal for 3 Weeks Before Death	Rate of IV Glucose (mg/kg/min)	Liver Weight at Autopsy (Per Cent Above Normal)
1	M	11	80	0	yes	13.5	254
2	F	14	66	0	yes	14.8	246
3	F	10	86	0	yes	9.3	164
4	M	13	54	0	yes	10.8	309
5	F	16 mo	47	0	yes	17	291
6	M	10 mo	39	0	yes	17	324
7	M	3	85	0	yes	13.1	440
8	F	4	70	0	yes	14.3	331

levels of glucose infusion for periods longer than one to two weeks) is an adenosine triphosphate (ATP) requiring conversion to fat and the production of CO_2 in excess of oxygen consumed.

The fact that the RQ is above 1 indicates that in a net sense all CO_2 production is coming directly or indirectly from glucose. Thus, some of the infused glucose directed to fat must then be oxidized as fat. Although we have no direct proof of this scheme, it is the only plausible explanation for the existence of a quasi-plateau in expired CO_2 enrichment. This is because the ^{13}C molecules must be going into a large enough pool so that they will be diluted to such an extent that subsequent oxidation of molecules containing those labeled carbons will not lead to a progressive rise in expired CO_2 enrichment over the time span of the experiment. Fat would seem to be the only likely candidate, although isotopic exchange with glycogen cannot be excluded entirely. Furthermore, glucose is a known stimulator of fat synthesis in the liver.[13] The presence of fat in the liver at autopsy is consistent with the concept of an increased fat synthesis during the glucose infusion. It is not clear why the normal transport mechanisms that are responsible for the translocation of triglyceride from the liver to the periphery were not adequate, but the fact that they were not (at least to the extent that the fat deposits accumulated) suggests a negative effect of extremely high glucose infusion rates.

The concept of physiological cost effectiveness is important here, for although increasing glucose loads do, in fact, increase CO_2 production directly from glucose, the increased net ATP production is small and outweighed by the increased respiratory work required to excrete the excess CO_2 and the energy required for lipogenesis, as well as the space requirements for fat storage in the liver. Furthermore, the administration of pharmacologic levels of glucose disrupts the normal hormonal and substrate profile of the blood, and this may have many subtle effects as yet unrecognized.[19]

Studies carried out relating the rate of protein synthesis to the rate of glucose infusion also support the concept of an optimal level of glucose infusion when examined on a physiological cost-effective basis. There is a statistically significant increase in protein synthesis with the higher levels of glucose infusion as compared to lower levels. However, when the higher levels of glucose infusion are divided into high and very high levels, no difference is present. The number of studies carried out to examine leucine rate of appearance and protein synthesis is not sufficient to allow evaluation of protein synthesis rates at small increases in rate of glucose infusion. It is probable, however, that as in CO_2 production from glucose, the protein synthesis rate at high levels continues to increase as the glucose infusion rate is increased. However, even if present, we believe that this small increase is offset by the above-mentioned problems caused by the conversion to fat of that portion of the infused glucose which is unoxidized.

The addition of exogenous insulin to a glucose infusion which had caused moderate hyperglycemia alone, although successful in returning the blood sugar toward normal, did not raise the rate of CO_2 production directly from glucose in the healthy male volunteers or in the burn patients studied (Table 3). Thus, any beneficial effect of insulin is not mediated through an enhancement of the direct oxidation of glucose.

The addition of insulin to the glucose infusion appeared to have affected protein synthesis differently from the way it affected glucose oxidation. Although the number of studies is small, the addition of insulin to glucose infusions sufficient to reverse the mild hyperglycemia toward a normal level of glucose produced a consistent increase in protein synthesis in patients 8–38 years of age; however, the increase was not statistically significant. The available data are insufficient to comment on the older age groups. It is known that sensitivity to insulin is altered in the elderly,[4] so that the response may be different from that seen in the young.

The possible increase in rate of protein synthesis in young patients when insulin is infused with glucose is not a surprising finding. However, it is of interest to note that the increased rate of protein synthesis does not appear to be mediated through an increase in glucose oxidation but perhaps is mediated directly through protein synthesis mechanisms.

Striking findings of this study were the two untoward effects, hepatomegaly produced by fatty infiltration and increases in the respiratory work load secondary to an elevated CO_2 production. Both of these effects we believe are directly related to very high glucose infusion rates over periods of several weeks in patients who were not in depleted nutritional state or starving at the beginning of the period of glucose infusion. These two problems, hepatomegaly and the increased respiratory work load, are both involved in producing degrees of respiratory failure, although mild liver function tests and abnormalities such as small elevations in the serum bilirubin, serum glutamic oxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH) and alkaline phosphatase indicate a degree of hepatic dysfunction, possibly secondary to a degree of intrahepatic obstruction. The respiratory abnormalities were more prominent in children, probably because the increase in liver size secondary to fatty infiltration produced a more marked elevation and fixation of the diaphragm and thus a more pronounced reduction in tidal volume than in the adult. However, we have noted degrees of respiratory failure in adult burn patients, particularly in those patients who had pre-existing respiratory disease. In these patients oxygenation was not a problem even on room air, but the arterial P_{CO_2} was elevated, and occasionally correction demanded mechanical respiratory support. We believe that patients on room air who have hepatomegaly and mild liver function abnormalities together with a normal P_{O_2} and an elevated P_{CO_2} and who have been receiving a high glucose infusion over a period of weeks should be evaluated for metabolic as well as respiratory and hepatocellular abnormalities.

References

1. Allsop, J. R., Wolfe, R. R. and Burke, J. F.: The Reliability of Rate of Glucose Appearance In Vivo Calculated from Constant Racer Infusions. Biochem. J., 172:407, 1978.
2. Allsop, J. R., Wolfe, R. R. and Burke, J. F.: Tracer Priming the Bicarbonate Pool. J. Appl. Physiol., 45:137, 1978.
3. Albano, J. D. M., Ekins, R. P., Maritz, G. et al.: A Sensitive, Precise Radioimmunoassay of Serum Insulin Relying on Charcoal Separation of Bound and Free Hormone Moieties. Acta Endocrinol., 70:487–509, 1972.
4. Andres, R.: Aging and Diabetes. Med. Clin. North Am., 55:835, 1971.
5. Bier, D. M., Arnold, K. J., Sherman, W. R. et al.: *In vivo* Measurement of Glucose and Alanine Metabolism with Stable Isotope Tracers. Diabetes, 26:1005, 1977.
6. Gamble, J. L.: Chemical anatomy. *In* Physiology and Pathology of Extracellular Fluid. Cambridge, Mass. Harvard University Press, 1950.
7. Golden, M. H. N. and Waterlow, J. C.: Total Protein Synthesis in Elderly People: A Comparison of Results with (^{15}N) Glycine and (^{14}C) Leucine. Clin. Sci. Mol. Med., 53:277, 1977.
8. Gruenke, L. D., Craig, J. C. and Bier, D. M.: Multiple Ion Detection by Accelerating Voltage Alternation in Conjunction with Voltage Sweeping. Biomed. Mass Spectrom., 1:418, 1974.
9. Holmes, W. F., Holland, W. H., Shore, B. L. et al.: Versatile computer Generated Variable Accelerating Voltage Circuit for Magnetically Scanned Mass Spectrometers: Use for Assays in the Picogram Range and for Assays of Stable Isotope Tracers. Anal. Chem., 45:2063, 1973.
10. Issekutz, B., Jr., Paul, P. and Miller, H. I.: Metabolism in Normal and Pancreatectomized Dog During Steady-state Exercise. Am. J. Physiol., 213:857, 1967.
11. Kien, C. L., Young, V. R., Rohrbaugh, D. R. and Burke, J. F.: Increased Rates of Whole Body Protein Synthesis and Breakdown in Children Recovering from Burns. Ann. Surg., 187:833, 1978.
12. Matthews, D. E., Galim, E. B. and Bier, D. M.: The Rapid Determination of Stable Isotopic Enrichment in Individual Plasma Amino Acids using Chemical Ionization Mass Spectrometry. Anal. Chem., 51, 1979.
13. Nikkila, E. A.: Regulation of hepatic production of plasma triglycerides by glucose. Lundquist, F. and Tygstrup, N. (eds.): *In* Regulation of Hepatic Metabolism. New York, Academic Press, P. 360, 1974.
14. Segal, I. H.: Biochemical Calculations. 1st edition. New York, John Wiley & Sons, 1968.
15. Somogyi, M.: Determination of Blood Sugar, J. Biol. Chem., 16:69, 1945.
16. Steele, R.: Influence of Glucose Loading and of Injected Insulin on Hepatic Glucose Output. Ann. N.Y. Acad. Sci., 82:420, 1959.
17. Wilmore, D. W.: Nutrition and Metabolism Following Thermal Injury. Clin. Plast. Surg., 1:603, 1974.
18. Wolfe, R. R., Allsop, J. R. and Burke, J. F.: Glucose Metabolism in Man: Responses to Intravenous Glucose Infusion. Metabolism, 28:210, 1979.
19. Wolfe, R. R., Snowden, J. M. and Burke, J. F.: Influence of Insulin and Palmitic Acid Concentration on Pulmonary Surfactant Synthesis. J. Surg. Res. (submitted for publication).

DISCUSSION

DR. WILLIAM R. DRUCKER (Rochester, New York): As Dr. Burke pointed out, we are now in an era of cost containment and concern about costs, and this is not just a socioeconomic problem it's a biological problem and that, in essence, is the theme of his paper, as I heard it.

As he also mentioned, Dr. Gamble gave us the minimum standards for the administration of glucose. The 100 g/day keeps a normal, nonstressed individual out of ketosis. Dr. Burke is now looking at the other end of the scale: Can we overdo it? Is there such a thing as overnutrition?

Many in this audience know that Dr. Robert Alman, somewhere during the war and shortly thereafter, demonstrated that the administration of glucose can protect against protein loss up to a level of about 800 calories; after that it has very little effectiveness.

Later, Drs. William Abbott and William Holden in Cleveland demonstrated very clearly that patients can be kept in nitrogen balance if they receive essentially the same caloric, nitrogen and carbohydrate intake postoperatively as they received preoperatively.

Some time ago, Dr. Wilmar showed us that the size of the injury has a very direct effect on the demand for nutrition following injury.

The question here is: Just what is overnutrition? The technology used is very interesting, and I admit, frankly, I'm not really in a position to understand it fully, and that is something that I think in time will have to be looked at: Is this technique that was employed valid for the conclusions that are drawn?

I have two comments, and three questions. My comment is that, as far as insulin is concerned, the data obtained are exactly what I think one would expect. I doubt very much if insulin would have an effect on the oxidation, but it does have an effect on glucose uptake. Insulin is a banker hormone; it stores all the foodstuffs, fat, protein, and carbohydrate. In this instance, insulin allowed the glucose to enter the cell, and, in fact, there is a decrease in the level of blood glucose in the manuscript. What happens to the glucose inside the cell—I suspect, here it was more available to promote protein synthesis, rather than going in other pathways.

The next comment is that I would be concerned about the production of CO_2, and the conversion of glucose to fat, in terms of the consequences physiologically. To me, this is one of the most interesting aspects of the paper. Dr. Burke and his associates have shown that there may be very detrimental biological consequences by overnutrition in addition to the hyperosmolality that we all know about; that there can be an increased production of CO_2 which produces a respiratory demand on a patient that potentially is already overburdened because of the burn and other problems they have.

In addition, the glucose going to fat can cause an increased size of the liver, and cause respiratory embarrassment from that.

My questions, Dr. Burke, are these. Did you, as Dr. Wilmar has shown previously, demonstrate a relationship to your glucose tolerance, in effect, to the size of the wound? Does the wound constitute a demand for glucose—a primary demand for glucose—so that, in fact, your tolerance will go up as the burn size increases?

What is the source of this increased CO_2? Where does it come from, and what is its effect on energy metabolism?

I have enjoyed this paper very much. It's very well done. It's well written; and my only concern is that someone look at this technology carefully.

Dr. John H. Siegel (Buffalo, New York): I do have a couple of questions and comments.

The first is that Dr. Burke used the amino acid leucine which was labeled with C^{13}—that is, labeled on a carbon atom—and has attempted to infer from the fact that there is a reduced amount of labeled CO_2 produced from the labeled leucine in the presence of high glucose loads, that there was more protein synthesis under these conditions. However, he has also shown us that fat, derived from labeled glucose through acetyl CoA, may be the consequence of the increased metabolism of glucose, rather than CO_2 production through oxidation.

I wonder whether the leucine may also be going to fat, since it also has access to the 2-carbon fat synthetic pool through acetyl CoA, and perhaps what he is interpreting as protein synthesis may, in fact, simply be the diversion of ketogenic amino acid substrates into pools that are not really related to protein synthesis but to lipogenesis.

The second comment is that I think a lot of the data one sees under these substrate loading conditions depends on the kind of patient that one is studying, that is to say their physiologic state. Dr. Burke's group of burned patients look much like nonseptic trauma patients in terms of their physiologic parameters, and although they have some burn wound infection, they would appear to have minimal true sepsis. In this regard, I noticed by looking at his CO_2 data that they probably have very high oxygen consumption, since their RQ's are fairly high and their CO_2 production seems to be large. Also they are already in near or positive nitrogen balance, which puts them in the best group of septic patients on metabolic grounds.

This is the group of patients in whom I think one would expect to see the findings that Dr. Burke has shown. However, there is a group of patients who become severely septic, in whom oxygen consumption falls, and in this group of septic patients with inadequate oxidative metabolism it would appear that there is an enormous amount of gluconeogenesis. If one looks at these low oxygen consumption septic patients, there are large amounts of circulating alanine, which is the carrier amino acid for muscle NH_3 derived from branch chain amino acid catabolism. This suggests that there are other kinds of septic patients with large amounts of tissue breakdown and unrestricted gluconeogenesis, since glucose also rises in this type of patient.

In contrast to the patients described by Dr. Burke, this group of severely septic patients, with low oxygen consumption, cannot effectively have their circulating glucose levels reduced by insulin. In fact, these people show an exaggerated gluconeogenesis syndrome in spite of insulin.

The final comment is to note the fact that if one uses labeled leucine as a marker, the leucine which is important is the leucine which one does not see. The unseen leucine is the structural leucine in peripheral muscle tissues which is liberated by catabolism. It is metabolized first by transamination with pyruvate, and large amounts of carrier amino acids like alanine, glycine, and glutamine are produced, and yet one would not see this amino acid as leucine, in terms of enlarging the leucine pool, and yet the three carbon fragment originally from leucine is, of course, a major source for glyconeogenesis, and via hepatic metabolism of alanine an oxidative or lipogenic substrate.

I wonder if Dr. Burke would comment on these issues.

Dr. Basil A. Pruitt, Jr. (Fort Sam Houston, Texas): I'd like to present some confirmatory data recently generated by Dr. Wilmore, (slide) indicating that the glucose needs of the burn patient and the effect of glucose infusion relate directly to metabolic rate and burn size. You can see that the infusion of glucose at a rate of 2 mg/kg/min reduces hepatic gluconeogenesis in the control patients, while there is still a significant hepatic vein/arterial difference in the burn patients. Although a definite decrease in hepatic glucose production occurs with glucose infusion in hypermetabolic patients it is not to the same extent as in the control patients with lower metabolic rates.

(slide) Since the metabolic rate of patients with burns is related to the size of the burn, as depicted here, I would ask Dr. Burke how glucose utilization in his patients was related to burn size.

(slide) Lastly, I would take issue with the comment that what the authors call cost-effectiveness is a superior assessment of nutritional adequacy as compared with simple nitrogen excretion rate. Dr. James Long, some years ago, showed that in patients with burns nitrogen excretion plateaued at a minimum when the carbohydrate intake/metabolic rate ratio approached 1. A glucose infusion rate of 6 mg/kg/min, as in Dr. Burke's patients, represents about 0.8 of the resting metabolic needs of a 70 kg man with a 50% burn. That data point would be located on this nitrogen excretion curve near the inflection point and such is reflected in Dr. Burke's data. I therefore, think that one can come up with the same assessment of nutritional adequacy using just nitrogen excretion data in burn-injured patients.

Dr. Stanley M. Levenson (Bronx, New York): The questions asked by Burke and his colleagues are straightforward, but the techniques required to answer the questions are far from straightforward. There are a number of assumptions which must be made in the tracer methodology employed, and Burke and his associates have gone to great lengths in their prior work to establish the validity of the assumptions.

I would like to comment briefly on their observations regarding the occurrence of hepatomegaly caused by fat accumulation, seemingly associated with the infusion of large amounts of glucose. Their observations were in children, but presumably the same would hold for adults.

In their paper the authors state: "It is not clear why the normal transport mechanisms that are responsible for the transfer, or translocation, of triglyceride from the liver to the periphery were not adequate." I would like to offer two speculative suggestions.

1) It is known experimentally that large amounts of glucose will interfere with the action of the lipid mobilizing factor produced by the pituitary gland.

2) It occurs to me that it is possible, though the data are not given in Burke's paper for me to determine this, that there may have been an inadequate choline intake by these individuals. When patients are fed parenterally, the only significant source of choline would be from intravenous fat emulsion and the chances are that the amount the patients receive may be inadequate. We know that if there is inadequate choline intake, fat begins to accumulate rapidly in the liver. This is an area which we really do not know enough about how much choline to put into the intravenous mixture to make it optimal for seriously ill and injured patients. Burke's patients received no intravenous fat emulsion during the study periods. It is not stated whether they received fat emulsion or choline in some other form in the periods preceding the study periods.

I would like to now pass briefly to ask Dr. Burke how the data regarding protein synthesis as related to the amount of glucose infused correlated with the measured caloric expenditure by the patients. As I calculated the intakes given during the various study periods, the caloric intake was roughly 25 calories per kilogram body weight during the period of low level glucose infused, 50 calories per kilogram body weight during the midlevel period and 70 calories per kilogram body weight at the high level of glucose infusion. I suspect that in terms of the measured caloric expenditure, it would turn out that 25 calories per kilogram body weight was much too low to meet the caloric expenditure, and therefore one would anticipate that as one increased the glucose infused, one would get an increase in protein synthesis until the caloric intake was significantly greater than the caloric expenditure, a point which was probably reached at a level below the 70 calories per kilogram intake, the highest level infused by Burke and his colleagues. This point was likely not too far above the midlevel of caloric intake.

Finally, in the full written paper Dr. Burke mentions that the data regarding the optimal amounts of glucose infused would probably vary depending on the amount of amino acids infused with it; I am sure that is correct. I would like to point out that the level used by Burke and his associates during the study periods, 1.33 gm of protein per kilogram body weight, is substantially less than what has been found in a large number of studies to be required by the burn patient at a reasonable caloric intake for maximal long-term positive nitrogen balance, which, when corrected for urea accumulation, reflects protein synthesis.

I noted that Burke's patients, except for during the study periods, had protein intakes about twice as high as were given during the study period.

The last question that I would like to ask Dr. Burke is whether he noted any differences in caloric expenditure as the amounts of glucose infused were increased. I mention this because about 50 years ago DuBos, Schaeffer and Coleman in their studies of patients with serious infections with oral diets noticed that the amounts of calories that had to be given for near maximal protein utilization were significantly higher than the resting caloric expenditure measured at lower caloric intakes.

Dr. Francis D. Moore (Boston, Massachusetts): There was an old saying that "fat burns in the flame of carbohydrate"; tiny amounts of sugar prevent ketosis. We have come to realize in the last few years that "peptide bonds are forged in the furnace of carbohydrate," and that that metabolic heat, ATP, is essential for protein synthesis. The fuel in the furnace must be regulated pretty carefully.

It might be helpful to calculate the data that Dr. Burke has shown us, to help our everyday clinical thinking. Approximately 1.33 mg/kg/min of amino acids, about 100 g/day in a 70 kg adult, which is about 3.1 of the regular central vein mix that most of us use is, fundamentally, that originally used by Dr. Dudrick. Giving the glucose at the rate of his Group II, it figures out to about 600 g of glucose/day, which is about 3.1 of the 400/600 central vein mix that we usually use.

That equals out to a calorie/nitrogen ratio of 180 nonprotein calories per gram of nitrogen, which is a little bit lower than we had thought was ideal. We had been shooting for 200–220.

He has shown us the satiety syndrome, or fatty liver. I think everyone who has worked in this field has shown that you can give too much rich intravenous food and get all sorts of effects. We found that humans given too much glucose (*i.e.*, supracaloric amounts) had pain in the right upper quadrant and disordered liver functional tests; obviously, we stopped the study then.

It is interesting in this connection that fatty livers can be produced by excessive fat oxidation from within the body. An example is weight loss after jejunoileal bypass, in which no glucose is given whatsoever. Fatty livers can come from other sources involving unbalanced caloric availability, and I would wonder, and ask Dr. Burke, if that could not enter into some of their calculations.

On the insulin added, it is interesting to compare Dr. Burke's data with those of Hinton and Allison, the British workers who did so much work with huge amounts of insulin. Dr. Burke used very small amounts of insulin. The plasma insulin concentrations in these subjects were already 50–60 microunits, which is what we would expect in persons given this much carbohydrates. The normal pancreas produces plenty of insulin, and if you give small additional amounts, you are probably not going to get a big additional effect. The British workers gave huge amounts.

Dietitians and nutritionists have been saying that we need to give people a balanced diet for years. This paper strengthens the view that when diet is given intravenously it should also be balanced regarding carbohydrate and protein precursors, perhaps fat also.

Dr. John F. Burke (Closing discussion): To answer at least some questions, I will begin with glucose tolerance. The relation of the glucose tolerance test to glucose turnover and to burn size is an interesting problem. In our evaluation of the glucose tolerance test we have demonstrated that it does not give reliable information on the exact level of glucose turnover. Although these patients would have an abnormal glucose tolerance test it would not necessarily mean that they had an abnormal rate of glucose clearance from the blood. We have therefore chosen to measure glucose kinetics directly using tracer methodology in the isotopic steady state. None of our calculations include glucose tolerance test data.

The source of the CO_2 raising the RQ, at least in our mind, is related to lipogenesis from glucose. This metabolic pathway produces CO_2 without a comparative production of ATP. The excess CO_2 generated must be excreted at an energy cost for the additional respiratory work.

We used leucine in our studies because it not only was useful for a number of other studies but also for technical isotope reasons. Although there is probably a small amount of the leucine carbon skeleton converted to fat it does so after decarboxylation and is therefore assumed to be oxidized because the label appears as CO_2. It does not raise the estimation of protein synthesis. I say this with some certainty because our N^{15} data in these patients gives us the same protein synthetic rate. I believe that within the errors of the system we are observing protein synthesis when 1 ^{13}C leucine is used as a tracer molecule.

It is important to recognize that the studies reported are whole body leucine turnover, CO_2 production and protein synthesis rates. These are not studies of an organ, or any organ system. Internal cycles such as conversion of glucose to alanine and alanine back to glucose would not be seen in this type of study. In other studies we have demonstrated that these patients have a large lactate turnover, but this metabolic reaction is not seen using uniformly labeled C^{13} glucose because none of the carbons are oxidized during the recycling.

The rate of suppression of gluconeogenesis in the liver produced by exogenous glucose is variable in burned patients but on the whole we have found it not markedly different from normal volunteers. It is our feeling that the normal regulation of the blood glucose level is obtained by modulating glucose production in the liver. In the burned, nonseptic patient this regulation is present, but it is decreased. For example, in a normal person near maximum suppression of gluconeogenesis can be obtained at a glucose infusion rate of, say, 2 mg/kg/min. In the burned, nonseptic patient, in our experience, it is somewhere around 5 mg/kg/min.

Concerning choline production I cannot comment specifically except to say that in the patients in whom it was measured the level was normal. Fat does occur in the liver in at least some patients who die of injury or sepsis, but I do not think it is seen at the extensive level seen here, unless the patient has received extensive levels of glucose infusion.

Therapeutic Approaches to Anergy In Surgical Patients

Surgery and Levamisole

JONATHAN L. MEAKINS, M.D., NICOLAS V. CHRISTOU, M.D.,
HARRY M. SHIZGAL, M.D., LLOYD D. MACLEAN, M.D.

From the Departments of Surgery and Microbiology,
Royal Victoria Hospital and McGill University,
Montreal, Quebec, Canada

Skin tests (ST) in 1332 patients are associated with increased morbidity from sepsis. Patients with normal skin tests had a 7% major sepsis rate and 2% mortality rate. Thirty-six per cent of anergic (A) patients and 21% of relatively anergic (RA) patients died; 52% of A patients and 34% of RA patients had sepsis. These data include all patients studied and represent their worst skin test. Two studies were done. The first was a retrospective evaluation of effect of surgery upon 49 anergic patients with biliary tract disease, colon cancer, bowel obstruction, hypovolemia and visceral abscesses. The patients did not receive total parenteral nutrition (TPN). The data show that surgery without TPN can reverse the anergic state and did so in 84% of patients reported. The second study was a prospective, double-blind, randomized trial of the effect of levamisole on skin tests, neutrophil chemotaxis (CTX), sepsis and mortality in 39 preoperative anergic patients. Major sepsis was significantly increased in placebo group ($p < 0.05$). Mortality, minor sepsis, restoration of skin tests and chemotaxis were somewhat better in levamisole patients but not statistically so. These studies show that in addition to TPN, surgery and immunorestorative drugs are viable approaches to the management of selected anergic patients.

THE FAILURE OF DELAYED hypersensitivity responses, or anergy, has proven to be a marker for altered host resistance, sepsis and mortality in surgical patients.[15,17] The etiology is varied and often multifactorial. Factors implicated as causes of anergy are age over 80, cancer, sepsis, shock, major trauma and malnutrition.[9,16,18] The varied etiology suggests that treatment must similarly be varied and directed to the specific cause of anergy. There has been a tendency to associate anergy and malnutrition. This appears correct in about one-third of patients.[21] This paper examines in a retrospective manner the effect of surgery upon anergy and its resolution and prospectively evaluates the use of levamisole on immune restoration and outcome in preoperative patients with altered skin tests.

Materials and Methods

Skin Testing

Skin testing was performed using an intradermal injection of each of five recall antigens: purified protein derivative (PPD), 5 toxic units (T.U.)/0.1 cc (Connaught Laboratories, Willowdale, Ontario); mumps skin test antigen, undiluted (Eli Lilly Company, Indianapolis, Ind.); candidin, 1:100 (Hollister-Stier Laboratories, Mississauga, Ontario); trichophytin and streptokinase-streptodornase (Varidase®), 1000 units/cc (Hollister-Stier Laboratories, Mississauga, Ontario). In addition, a control solution of buffered diluent, (Hollister-Stier Laboratories) was used. Syringes were prepared with 0.1 cc of each solution immediately before injection. All tests were administered and read by one person. The diameter of induration in millimeters at 24 and 48 hours following injection was measured and recorded. A skin test was considered positive if the induration at either reading was 5 mm or greater. The patients were classified according to their response to the five recall antigens as follows: normal (N), two or more positive; relatively anergic (RA), one positive; or anergic (A), no positive responses. Skin testing was repeated weekly until each patient recovered, died or was discharged.

Neutrophil Chemotaxis

Neutrophil chemotaxis (CTX) was studied using a modified Boyden technique[3] and read using the leading-front method of Zigmond and Hirsch.[24] Nineteen

---

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

Reprint requests: J. L. Meakins, M.D., Royal Victoria Hospital, Room S6.24, 687 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1.

Supported by grants from the Ortho Pharmaceutical Company and The Medical Research Council of Canada.

0003-4932/79/0900/0286 $01.05 © J. B. Lippincott Company

laboratory and hospital personnel served as controls. Briefly, 10 ml of peripheral venous or arterial blood were mixed with heparin, 10 units/ml, and added to 2.0 ml Dextran 70® (Macrodex® 6% in normal saline, Pharmacia AB, Uppsala, Sweden) in 15-ml plastic tubes. Red blood cells settled in 45 min at room temperature, and the leukocyte-rich supernatant was washed twice and resuspended to a concentration of 5.0×10^6 neutrophils/ml in Gey's solution of pH 7.2–7.4. The viability of neutrophils was assessed by trypan blue exclusion and showed viability of greater than 95%. Sykes-Moore tissue culture chambers were modified with rubber gaskets and divided into upper and lower compartments of 0.5 ml capacity separated by a 3-μ Millipore® filter, 150 μ thick.

The upper and lower compartments were filled through separate ports using 25-gauge needles. The lower compartment was filled with a chemotactic attractant, casein, 5 mg/ml (Merck AG, Darmstadt, Germany), and the upper compartment with 0.5 ml of leukocyte suspension. The filters were removed, fixed in alcohol and stained with Harris hematoxylin. Using high power and a micrometer rack, five random fields were examined on each filter and the distance traveled by the leading front of neutrophils was measured in microns. Three chambers were examined for each patient; the chemotactic distance was the mean of these values.

Study Groups

The outcome of 1332 patients skin tested between July 1976 and May 1978 was recorded. Those skin tested were undergoing major surgery of a magnitude greater than cholecystectomy or had multiple trauma or required treatment in the Surgical Intensive Care Unit.

Effect of surgery on skin tests. Forty-nine patients who were anergic prior to an operation were retrospectively identified. Time to restoration of cutaneous responses was measured from the operation to the day the skin tests that converted were applied. The diagnostic groups together with age and sex are detailed in Table 1. With two exceptions (described in Results section), none received total parenteral nutrition (TPN) prior to postoperative recovery of their cutaneous responses.

Effect of Levamisole in preoperative anergic patients. **Plan.** The study was a randomized prospective double-blind trial of the value of levamisole (L) given to anergic preoperative patients. Upon admission to hospital or in a preadmission clinic, patients were skin tested. If patients were anergic or relatively anergic, consent was obtained, and the patient was enrolled. Outcome measures were determined from the time the patient entered into the study.

TABLE 1. *Epidemiological Data: Retrospective Study*

	No. Patients	Mean Age	M	F
Biliary tract surgery	11	64.5	6	5
Resection colon cancer	8	67.3	1	7
Drainage of intra-abdominal abscess	7	59.6	1	6
Repeated drainage of intra-abdominal abscess	4	51.0	3	1
Relief of bowel obstruction	5	64.4	3	2
Control of hemorrhage	5	39	4	1
Pancreatic pseudocyst	1	70		1
Ureteral drainage	1	66	1	
Necrotizing fasciitis	1	54		1
Surgery, discharged anergic	6	72	5	1
	49		24	25

Forty patients were randomized in a double-blind fashion into two groups of equal population. One group received levamisole, the other a placebo. Coding and assignment of medication were accomplished by Ortho Pharmaceuticals. Levamisole was supplied as 50 mg tablets in packages of 36 tablets. Placebo (P) of identical appearance and packaging was also supplied. A tear-off label indicated the drug code. The medication was administered in single doses on prescribed days and subsequently on the same two consecutive days each week until the patient was ready for discharge. The dose used was calculated on the basis of 2.5 mg/kg of levamisole and rounded off to the nearest 50 mg.

The two basic treatment programs of the protocol are outlined in Figure 1. Surgery could not always be delayed to determine the effect of levamisole alone upon skin test responses. Medications and skin testing were continued in the postoperative period.

Neutrophil chemotaxis was performed in 34 patients, 16 taking levamisole and 18 receiving placebo.

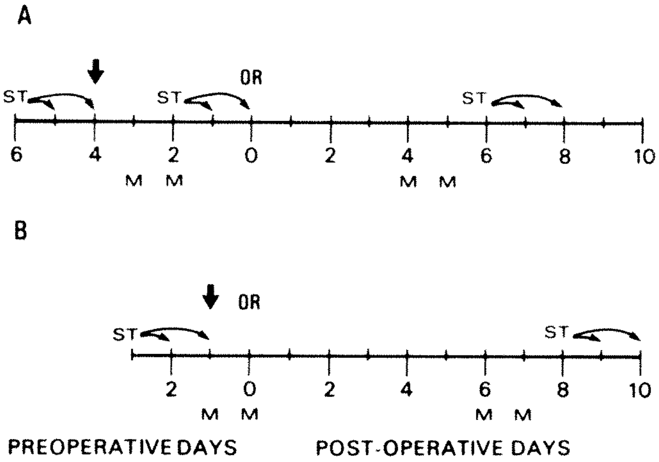


FIG. 1. The two basic study plans for administration of medication (M) (levamisole or placebo). Skin tests (ST) were applied as noted in relation to the operation (OR).

TABLE 2. *Skin Test Results in 1332 Patients*

Skin Test	Patients	Sepsis	Mortality
Normal	928	62 (7%)	21 (2%)
Relative anergy	125	43 (34%)	26 (21%)
Anergy	279	146 (52%)	100 (36%)

Outcome. Sepsis was defined as a visceral abscess at surgery or autopsy and/or positive blood culture. Pneumonia, wound infection and urinary tract infection were classified as other infections, and wound dehiscences were documented. Mortality was a hospital death.

Results

Skin Testing All Surgical Patients

The worst skin test result for 1332 patients was the basis of the results documented in Table 2. Patients who were anergic or relatively anergic at some time during their hospital course had a significantly higher rate of sepsis and mortality when compared to those with normal responses. Half of the anergic patients had sepsis, and one-third died. One-third of the relatively anergic patients had a septic episode, and one-fifth died.

Effect of Surgery on Skin Tests

The category of illness, number of patients in each category, mean age and sex distribution are documented in Table 1. The patients' courses in hospital are described in Tables 3–8 or in short case reports.

Biliary tract surgery. The diagnoses, operations and clinical details are listed in Table 3. Four patients were initially anergic and seven relatively anergic. Mean time to normal skin test response postoperatively was 5.7 days. Patients were discharged in an average of 12.6 days (range, 7–19 days). There was a single urinary tract infection and no other complication. Two patients had preoperative positive blood cultures and nine had positive bile cultures, all for multiple organisms.

TABLE 3. *Biliary Tract Surgery and Skin Test Responses*

					Classification			Microbiology			
Patient	Sex	Age	Diagnosis	Operation	A	RA	N	Blood	Biliary	Antibiotics	
1	M	68	Acute cholecystitis	Cholecystectomy CBDE		2d* →		Neg.	*E. coli* *C. welchii* *Klebsiella*	Ampicillin	T‡
2	F	72	Cholangitis	Cholecystectomy CBDE		4d →		Neg.	*E. coli* *Klebsiella* Enterococcus *Proteus*	Keflin®	T
3	M	68	Chronic cholecystitis	Cholecystectomy CBDE		4d →		†	*E. coli* *Citrobacter* div.	Keflin	P§
4	F	74	Acute cholecystitis Cholangitis	Cholecystectomy CBDE		5d →		*E. coli*	*E. coli* Enterococcus	Penicillin Gentamicin	
5	F	70	Acute cholecystitis Cholangitis	Cholecystectomy CBDE	5d →			Neg.	*C. welchii* *E. coli*	Ampicillin	T
6	M	38	Obstructive jaundice Cholecystitis	Cholecystectomy CBDE	7d →			†	*S. epidermidis* *Streptococcus*	Keflin	P
7	F	48	Cholecystitis Cholangitis Cholecystoduodenal fistula Lesser sac abscess	Cholecystectomy CBDE Fistula closure Abscess drainage	8d →			*S. viridans*	*Klebsiella* *S. viridans*	Ampicillin	T
8	M	73	Chronic cholecystitis	Cholecystectomy CBDE	6d →	7d →		Neg.	†	Ampicillin	P
9	M	63	Acute cholecystitis	Cholecystectomy		5d →		Neg.	*E. coli*	Keflin	P
10	M	69	Acute cholecystitis	Cholecystectomy		6d →		†	*S. epidermidis*	Keflin	P
11	F	56	Obstructive jaundice Ca. Pancreas	Choledochojejunostomy		4d →		†	Neg.	Keflin	P

* d = days.
† Culture not done.
‡ T = Therapeutic course.
§ P = Preventive.

TABLE 4. *Resection of Bowel Cancer and Skin Test Response*

Patient	Sex	Age	Diagnosis	Stage	Operation	Classification A	Classification RA	Classification R	Discharged Days Postop.
1	M	62	CA. r. colon	B	R. hemicolectomy		⊢ 3d† →		8
2	F	80	CA. rectosigmoid	C	Ant. resection*		⊢ 3d →		14
3	F	77	CA. l. colon	B	L. hemicolectomy		⊢ 5d →		9
4	F	66	CA. rectosigmoid	B	Ant. resection		⊢ 6d →		14
5	F	73	CA. r. colon	C	R. hemicolectomy	⊢ 3d →			11
6	F	66	CA. caecum	B	R. hemicolectomy	⊢ 8d →			17
7	F	56	CA. r. colon	D	R. hemicolectomy	⊢ 2d →	⊢ 9d →		9
8	F	72	CA. l. colon	C	Ant. resection	⊢ 7d →	⊢ 7d →		18

* Ant. = anterior.
† d = days.

Antibiotics were given therapeutically in five and preoperatively for prophylaxis in six.

Resection of colon carcinoma. Eight patients were anergic or relatively anergic at time of colon resection (Table 4). There were seven females and one male, with mean age of 69 years. The cancers in two patients were almost completely obstructing the colon. The cancers were Stage B in four, Stage C in three and Stage D in one. In six patients skin test responses improved from anergic/relatively anergic to normal in 4.7 days. Two anergic patients became relatively anergic in 4.5 days and normal in another 8 days. Patients were discharged in an average of 12.5 days. All received prophylactic antibiotics. There were no infections and no deaths. The patient with Stage D carcinoma died 5 months later.

Relief of bowel obstruction. Five anergic patients, three males and two females, of mean age 64.4 years recovered normal skin test responses following relief of bowel obstruction (Table 5). Two patients had complicated postoperative courses. One patient, in hospital 55 days postoperatively, developed a wound infection, urinary tract infection, pneumonia, two bouts of septicemia and required three courses of cloxacillin and gentamicin. The second, discharged 74 days postoperatively, had a wound infection and two urinary tract infections, each requiring a course of cephalothin or gentamicin.

Correction of hypovolemia. Five patients, four males and one female, of mean age 39 years were anergic at the time of admission for upper gastrointestinal hemorrhage (Table 6). Three had bleeding esophageal varices; one stopped with transfusion alone, and a second, who had had neonatal portal vein thrombosis and was a heavy drinker, required a Sengstaken-Blakemore tube for control of bleeding. The third, who had had normal skin tests 5 weeks earlier following a failed mesocaval shunt, was anergic, in coma and actively bleeding from varices at the time a portocaval shunt was performed. The skin tests returned to normal 5 days later, and he was discharged 19 days postoperatively. Four of the five patients had infections requiring antibiotics. Transfusion requirement ranged from 4 to 19 units of blood. All were discharged home on an average of 17 days after admission with normal skin tests.

Drainage of intraabdominal sepsis. **Resolution with single drainage procedure.** Seven patients, six females and one male, of average age 59.1 years had restoration

TABLE 5. *Relief of Bowel Obstruction and Skin Test Responses*

Patient	Sex	Age	Diagnosis	Operation	Classification A	Classification RA	Classification N	Discharge
1	M	52	Small bowel obstruction	Lysis adhesions	⊢ 6d* →			55 d*
2	F	83	Postop. duodenal obstruction	Duodenojejunostomy	⊢ 7d →			12 d
3	M	47	Radiation enteritis	Jejunal resection	⊢ 8d →			11 d
4	M	78	Gastric outlet obstruction Cancer	Gastrojejunostomy	⊢ 6d →	⊢ 5d →		13 d
5	F	62	Rectosigmoid obstruction Cancer	Transverse colostomy	⊢ 3d →	⊢ 6d →		74 d

* Day 5.

TABLE 6. *Control of Hemorrhage and Skin Test Responses*

					Admission			Fluids*			Classification			Infection/	
Patient	Sex	Age	Diagnosis	Treatment	P	BP	HCT	WB	PC	P	A	RA	N	Infection/ Complication	Treatment
1	M	22	Varices: congenital, alcohol Gastritis	Cimetidine Pitressin Sengstaken-Blakemore tube	100	150/90	25	12	4	3	├	7d	→	Urinary tract infection	Keflin
2	M	60	Varices: alcohol	Transfusion	108	150/100	26	3	2	2	├	6d	→	Pneumonia Resp. arrest	Penicillin
3	M	44	Duodenal ulcer	Transfusion	100	110/70	27.3	2	2		├	6d	→		
4	F	52	Leiomyoma, Small bowel	Transfusion	128	170/90	21	3	3		├	5d	→	Urinary tract infection	Amoxacillin
5	M	19	Varices: cirrhosis Cystic fibrosis	Sengstaken-Blakemore tube Portocaval shunt	120	100/0	13	10	9	3	├	5d	→	Pneumonia	Penicillin Gentamicin

* WB = whole blood; PC = packed cells; P = plasma.

of ST responses following drainage of an intra-abdominal abscess. There were no recurrences. Two abscesses were associated with diverticulitis, one was a pelvic abscess following pancreatitis, and four were postoperative. Average time after drainage to improvement of ST was 5.4 days and to N responses 8.1 days (Table 7). Patients were discharged with normal skin tests at a mean of 20 days after drainage.

Recurrent drainage and conversion. There were four anergic patients who had multiple drainage procedures. Two recovered normal responses after a second or third drainage procedure. Two other anergic patients died anergic after two and three drainage procedures with residual undrained abscesses. Brief summaries follow:

Patient 1. A 61-year-old man had a cholecystectomy, hydatid cyst resection, gastric bleeding and drainage of a subphrenic abscess in the 3 months prior to admission with a residual biliary fistula. An abscess was drained through the fistula site, and subsequently at exploration a lesser sac abscess was drained which contained mixed flora. He remained anergic through a protracted septic course, with three separate septicemias, for 33 days until spontaneous drainage of a 1700 cc abscess. Skin tests became normal in 6 days, and he was discharged a month later. He received TPN for 33 days prior to skin test conversion to normal.

Comment

TPN allowed him to survive these complications; however, ST became normal only after drainage of the last abscess.

TABLE 7. *Conversion of Skin Tests Following a Drainage Procedure*

					Classification				Discharge
Patient	Sex	Age	Type of Abscess	Operation	A	RA	N	Microbiology	Days after Drainage
1	F	70	Pelvic, after total colectomy	Drainage per vagina		├ 1d*	→	Enterobacter	7d*
2	F	53	Pelvic, after postpancreatitis	Drainage		├ 5d	→	Mixed flora	9d
3	F	49	Pelvic, after abdominosacral resection	Drainage		├ 5d	→	*E. coli*	9d
4	M	63	Peridiverticular diverticulitis	Drainage Resection Colostomy	├	6d	→	Neg.	9d
5	F	67	Huge pelvic Peritoneal diverticulitis	Drainage Colostomy		├ 13d	→	Mixed	58d
6	F	61	Subphrenic, after gastrectomy	Drainage	├ 3d	→ ├ 8d	→	*E. coli*	31d
7	F	54	Subphrenic, after gastrectomy	Drainage	├ 5d	→ ├ 9d	→	Mixed	17d

* d = days.

Patient 2. A 27-year-old woman was admitted in a septic and anergic condition 3 weeks following appendectomy for a perforated appendix and drainage of a periappendiceal abscess. She had drainage of an intra-abdominal abscess but remained anergic. Nine days later a left subphrenic abscess was drained, and skin tests returned to normal 6 days later.

Patient 3. While anergic this 50-year-old man had a pancreaticoduodenectomy for carcinoma of the ampulla of Vater. He had a complicated postoperative course, with wound infections and septicemia. Twenty-three days later a left subphrenic abscess was drained. His course remained complicated with on-going sepsis to discharge 47 days later, during which time he received 20 days of TPN. He was readmitted anergic for two further drainages of subphrenic abscesses. He died a septic death 147 days after pancreaticoduodenectomy with intraperitoneal abscess.

Comment

The protracted course of this patient may be explained by inadequate drainage. More aggressive use of TPN might have helped; however, complete drainage is essential.

Patient 4. A 55-year-old man was anergic following removal of a retained common duct stone. He had gastric bleeding and was explored with the finding of a perforated duodenum and intraabdominal abscesses. Seventeen days later, still anergic, multiple abscesses were again drained, and a T-tube was placed in the common bile duct. The patient died 3 days later, and the autopsy showed peritonitis, further abscess formation and evidence of generalized sepsis.

Miscellaneous operations. Three patients with various conditions responded to surgery with conversion of skin tests to normal. One patient died of continuing sepsis. Nine days following drainage and debridement of a necrotizing fasciitis the skin tests of an anergic 54-year-old woman became normal. A 70-year-old relatively anergic male had *Escherichia coli* septicemia and an obstructed right ureter. Skin tests returned to normal 24 hours after retrograde catheterization of the obstructed ureter, with drainage of pus, followed by ureterolithotomy. A 66-year-old woman who originally had normal skin tests became anergic 13 days following left hepatic lobectomy for cholangiocarcinoma. A left upper quandrant infected pancreatic pseudocyst containing biliary material was drained. Her skin tests returned to normal 5 days later and remained normal for 8 more days, after which no further testing was done. She continued on a febrile septic course and died of sepsis from ascending cholangitis.

Comment

These three patients represent drainage of infection followed by restoration of skin test responses. The patient who died of sepsis might have become anergic again if she had been followed longer.

Patients discharged anergic following surgery. Six patients of average age 72.7 years, four with cancer, were found to be anergic or relatively anergic preoperatively. In none were their skin tests changed (Table 8). Four of the six had infectious complications. The relatively anergic patients were discharged in 8.5 days, one of whom died 6 months later. The anergic patients were discharged at an average of 23.8 days postoperatively; one died 2 months later.

Recovery of skin test and PMN chemotaxis. Neutrophil chemotaxis was measured when 11 patients were anergic and again in the postoperative period when their skin tests were normal. The skin tests improved

TABLE 8. *Discharged Anergic Following Surgery*

Patient	Sex	Age	Diagnosis	Operation	Skin Test	Complication	Discharge Days Postop.
1	F	55	Status post colon resection and abscess drainage for diverticulitis	Colostomy closure	RA–RA		9
2	M	79	CA. stomach, unresectable	Laparatomy Biopsy	RA–RA	Urinary tract infection	10
3	M	64	CA. pancreas Pyloric obstruction	Gastroenterostomy	A–A		9
4	M	74	CA. rectum, recurrent	Abdominoperineal resection	A–A	Infection of abdominal wound, perineal wound	42
5	M	78	CA. esophagogastric junction	Laparotomy Biopsy Esophageal dilatation	A–A	Wound dehiscence	21 (Convalescent home)
6	M	86	Motor vehicle accident Perforated bowel Dehiscence Pelvic abscess	Resection Drainage closure	A–A	Pulmonary embolus Urinary tract infection	23

TABLE 9. *Sepsis and Mortality*

	Levamisole (19)	Placebo (20)
Mortality	2 (10%)	5 (25%)
Sepsis	3 (16%) —*—	9 (45%)
Improved skin test	14 (74%)	12 (60%)
Improved chemotaxis	11/16 (69%)	9/18 (50%)

* $\chi^2 = 3.90$ $p < 0.05$.

in seven, remained abnormal in three and normal in one. When anergic the mean chemotaxis was 99.2 μ and improved significantly when skin tests became normal to 112.4 μ ($p < 0.025$).

Levamisole in Preoperative Anergic Patients

Among the patients skin tested preoperatively, 40 were identified as anergic or relatively anergic and consented to be part of the study. One patient, a 39-year-old relatively anergic female to be operated on for bilateral occlusive ileofemoral disease, discharged herself from the hospital 2 days after receiving levamisole and was dropped from the study. There were 19 patients in the levamisole group, 5 males and 14 females, with a mean age of 66.6. All had gastrointestinal diseases; eight had cancer. There were eight males and 12 females in the placebo group, with a mean age of 68.3 years. Eleven of these patients had cancer; the remainder had gastrointestinal problems.

In three patients drug sensitivities were suspected. One patient had cholestatic jaundice on liver biopsy at the time of cholecystectomy and common bile duct exploration. The code was broken, and the patient was on levamisole. She had been jaundiced when she received her two preoperative doses. On the day of surgery a patient who had received two doses of levamisole developed a rash which was thought to be due to a penicillin allergy. He received two more doses of levamisole without complications. A third patient, who had received eight doses of levamisole developed a rash on her legs. All medications were stopped, and she did well.

TABLE 10. *Nature of Sepsis*

1. Blood: *S. epidermidis*	1. Blood: a) *S. epidermidis* b) enterococcus
2. Subphrenic abscess	2. Blood: *S. epidermidis*
3. Intraperitoneal abscess Blood: Bacteroides Salmonella	3. Blood: *S. aureus* β-hemolytic *Streptococcus*
	4. Blood: *E. coli**
	5. Blood: *S. viridans**
	6. Blood: *Bacteroides**
	7. Blood: *Bacteroides* *S. epidermidis* Paracolonic abscess
	8. Pelvic abscess
	9. Peridiverticular abscess*

* Died.

One patient in each group had no procedures. A 71-year-old woman thought to have obstructive jaundice developed liver failure and died of a myocardial infarct. She received two doses of levamisole. An 87-year-old woman with pyloric obstruction received two courses of placebo. She initially was managed non-operatively and then refused surgery. Her course of TPN was terminated with a temperature of 40°, which was not associated with positive blood cultures and was not noted as a septic episode.

The only statistically significant difference in results (Table 9) was in sepsis rate. In levamisole patients, there were three septic episodes compared to nine in placebo patients ($p < 0.05$; $\chi^2 \times 3.90$). The other improved results in the levamisole group, fewer deaths and increased numbers with improved skin tests and polymorphonuclear leukocyte chemotaxis, did not achieve statistical significance.

Of the two deaths in the levamisole group, a 71-year-old woman dying of myocardial infarction with obstructive jaundice has been described. The other was a 95-year-old woman with angina who died 1 week after repair of wound dehiscence following cholecystectomy, common bile duct exploration and choledochoduodenostomy for acute cholecystitis and common duct stone. There were five deaths in the placebo group. Two were related to cancer, one patient died of metastases from carcinoma of the colon following hepatic artery cannulation and the other of gastric hemorrhage 10 days following exploration for an unresectable leiomyosarcoma of the stomach. Two patient deaths were directly related to sepsis, both following colon surgery. The fifth death was the result of both cancer and infection.

Sepsis rates as defined by intraabdominal abscess or positive blood culture were statistically different in the levamisole and placebo patients (Table 9 and 10). Three levamisole patients has a septic episode, one in association with a preoperative TPN line, the second with a subphrenic abscess after gastrectomy and the third with septicemia and abscess following ligation of the middle colic artery and colon infarction after gastrectomy.

There were nine septic episodes in the Placebo group; six were positive blood cultures and three abscesses. Two were related to original disease (Patients 7 and 9; Table 10). Diverticulitis with abscess occurred in one patient who died 2 days following a Hartmann procedure and 7 seven days after being enrolled into the study. The other, with positive blood cultures preoperatively, had a perforated cancer of the sigmoid found at surgery. The patient had received two doses of placebo and been in the study for 3 days. Three patients had positive blood cultures preoperatively (Patients 3,4,and 5 Table 10); two died. Four patients were septic in the postoperative period. One died of sepsis. In one patient, septic postoperatively, there were two separate septicemias (Patient 1, Table 10). These were counted as a single septic event for statistical purposes.

Positive cultures on IV catheter tips were not included as septic episodes unless blood cultures were positive. There were three episodes in which CVP tips were culture positive, all for *Staphyloccus epidermidis* and all with negative blood culture. Two were in the placebo group, and one patient had received levamisole. One other placebo patient had a temperature to 40° and lysis following removal of TPN line, with negative cultures.

Infections other than the previously defined septic episodes were also greater in the placebo group. There were five urinary tract infections in levamisole patients and eight in the placebo group. Pneumonia occurred in one levamisole and two placebo patients. Wound infection developed in two levamisole and six placebo patients. The only complication greater in the levamisole group was wound dehiscence; there were three compared to one for placebo patients.

The use of preventive antibiotics in the preoperative period was nine in patients receiving levamisole compared to 11 in the placebo group. Therapeutic courses of antibiotics were greater in placebo patients, 12 compared to six in those receiving levamisole. The use of multiple courses of antimicrobial drugs was similarly greater, six in Placebo patients and two in levamisole patients. Antibiotic use for therapeutic purposes was increased in patients receiving placebo.

Evolution of Immunological Parameters

Following inscription into the study skin tests improved in 14 levamisole patients (74%) and 12 placebo patients (60%). Neutrophil chemotaxis improved in 11 of 16 levamisole patients (69%) studied and nine of 18 placebo patients (50%). The values of PMN chemotaxis are graphed in Figure 2. The marked improvement of chemotaxis coincident with surgery in the placebo patients suggests that the underlying disease was responsible for the immunosuppressed state.

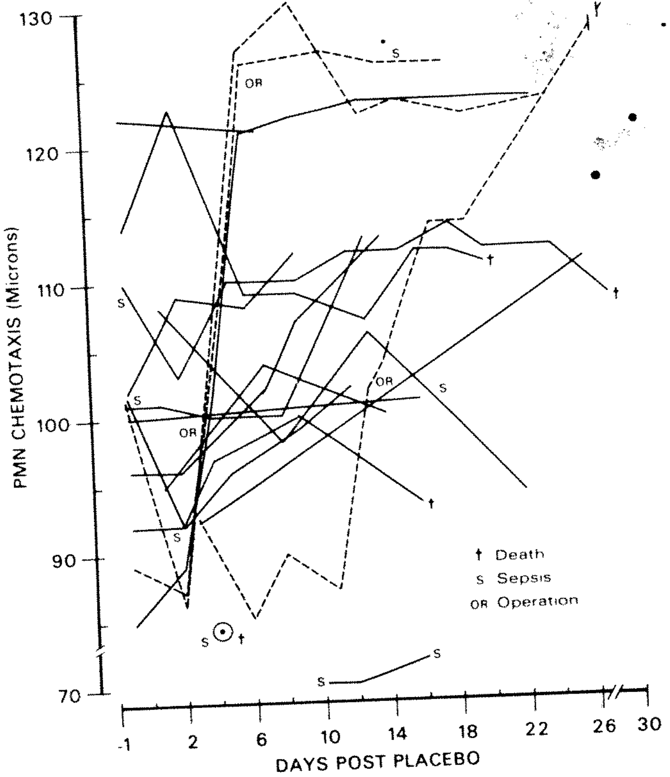


FIG. 2. The consecutive neutrophil chemotaxis value for each patient in placebo or levamisole groups. S = sepsis, † = death, or = operation.

Discussion

The importance of skin testing with recall antigens in the prediction of outcome in general surgical patients was first described by MacLean et al. in 1975.[15] The observations were extended in an additional 520 patients by Pietsch et al.,[18] and their prognostic value has been confirmed by others.[10,12] The 1332 patients herein described have not been previously reported. The ST in Table 2 reflects the worst response that each patient had while hospitalized. It is apparent that patients who are anergic or relatively anergic at anytime during their course in hospital are at major risk for sepsis and mortality. Many of the anergic and relatively anergic patients were identified following trauma, development of complications postoperatively or following emergency admission to the general surgical wards or surgical intensive care unit. The development of anergy in the postoperative period is an ominous sign and is generally secondary to sepsis or malnutrition. If the patients were followed serially with repeat skin tests at weekly intervals the information was especially useful to document the adequacy of treatment.[18]

In the initial stages of these studies,[15] nutritional defects appeared to be the significant etiological factor. The importance of malnutrition as a cause of depressed host resistance has been emphasized.[1,7] Other parameters suggestive of both malnutrition and immunodeficiency, serum albumin and absolute lymphocyte counts,[2,18] have been determined to be of prognostic value. There are data to suggest that anergy has a multifactorial etiology. Pietsch et al.[18] pointed out that advanced age, hemorrhage, trauma and sepsis itself as well as malnutrition could produce anergy. In cancer patients,[9] anergy has prognostic significance. Blunt trauma in otherwise healthy, well-nourished patients produces anergy and defects of neutrophil chemotaxis proportionate to the severity of injury and the age of the patient.[16] The variable etiology indicates that optimum therapy is also likely to require a variety of therapeutic approaches. Total parenteral nutrition is likely to benefit only the patients who have malnutrition as the principle etiologic factor of anergy.

In an attempt to further clarify the issue, the first study in this report, a retrospective one, examined the effect of surgery and other appropriate therapy in anergic and relatively anergic patients who had not received total parenteral nutrition. The patients studied were occasionally candidates for elective surgery but most often required an urgent or emergency procedure. It is clear in the presented patients undergoing biliary tract surgery, colon resection and relief of bowel obstruction that the operation contributed significantly to recovery of skin test responses. Nine patients with biliary tract disease had positive bile or gall bladder cultures (82%), which was higher than the expected 28% in this hospital,[14] suggesting that infection contributed to anergy in this group and its drainage led to restoration of skin test responses to normal. There was no infectious etiological factor in the two other groups. The management of gastrointestinal hemorrhage indicates that non-operative therapy as well as control of bleeding by surgical means can restore skin test responses. In these four groups of patients, anergy was associated with a specific acute surgical problem, the correction of which led to restoration of skin test responses without resorting to TPN.

Drainage of a septic focus was successful in restoring skin test responses in 12 patients. Two patients required multiple drainage procedures before recovery. One of these received TPN for 33 days while anergic. Responses were normal six days following spontaneous drainage of a 1700 cc intraperitoneal abscess. The deaths occurred in patients with undrained abscesses despite the use of TPN.

Drainage of infection or surgery did not always correct anergy. Six patients were discharged anergic or relatively anergic following surgery. Their ages were advanced, one had infection, and four had metastatic cancer, which might have accounted for their anergic state.

The discovery of the immunorestorative effects of levamisole was serendipitous.[19] The original observations have been extended into almost every field of medicine where restoration of the immune response could possibly contribute to prolongation of life. Levamisole is an agent which can restore skin sensitivities in the elderly,[20] cancer patients[22] and various nonmalignant diseases associated with decreased host resistance.[4] It is known to promote phagocytosis by neutrophils[8] and the reticuloendothelial system[1,23] and enhance neutrophil chemotaxis.[5] While restoration of cutaneous hypersensitivity responses appears important, alteration of the clinical course and a reduction in the prohibitive incidence of sepsis secondary to impaired immune responses is the major goal.

In the present study, the death rates in levamisole and placebo groups are not statistically different, although there were more deaths in the placebo group. The incidence of sepsis, as defined by a positive blood culture or visceral abscess, was significantly greater in the placebo group ($p < 0.05$). All other types of infections: urinary tract, pneumonia, wound, culture-positive CVP lines and negative blood culture-clinical episodes were increased in the placebo group as compared to patients who received levamisole. This apparently increased incidence of infection is substantiated by the increased therapeutic use of antibiotics in placebo patients, whether single or multiple courses were required. The only complication more frequent in levamisole patients was wound dehiscence.

If the difference is sepsis rate was a function of the drug levamisole, one would have expected that there would be a marked improvement in the immunological parameters, specifically, restoration of skin test and neutrophil chemotaxis. Improvement in skin tests in the levamisole group is marginally different from that of placebo, 74% to 60%. The number of patients improving in neutrophil chemotaxis is more convincing but not statistically significant.

There are four patients in the placebo group whose chemotaxis improved dramatically with their surgery (Fig. 2). The improvement in skin tests and PMN chemotaxis in placebo patients indicates that surgery alone can improve immune function. The significance of levamisole in augmentation of immune response is therefore unclear and worrisome with respect to decreased infection rates.

The failure of a clear-cut result in the levamisole study is the result of several factors. Anergy in surgical patients has a variable etiology, as seen in the retrospective study, and may be both the cause and the result of sepsis. Therefore, in a small study one might not get a response to a single agent, particularly when surgery can have an immunomodulation effect. The study numbers are small and differences not great. The dosage of levamisole might have been inappropriate. The *in vitro* effect of levamisole appears to block[5] the action of an inhibitor upon PMN chemotaxis.[6] The neutrophil has a short half-life, and it is possible that levamisole should be given daily to the anergic patient to ensure that all neutrophils are exposed to levamisole. However, there is evidence that clinically the patients receiving levamisole did better. Further data are required to clarify these points. The study should have a homogeneous larger population and more immunologic measures, both serum and cellular.

The patient who is anergic preoperatively continues to present a therapeutic dilemma. Should the surgeon operate or delay and institute TPN? Is the etiology at that time likely to be nutritional in origin? If it is, can TPN be depended upon to correct the problem? These studies with quantitative evidence of malnutrition in anergic, preoperative patients have not been performed. Patients who are found to be anergic following intensive surgery, surgery followed by complications and severe trauma are frequently malnourished and may respond favorably to TPN.

There are three possible therapeutic approaches to anergic patients. Surgery and specific nonsurgical treatments (restoration of blood volume, red cell mass, antibiotics, etc.), total parenteral nutrition and immunorestoration. The challenge for the future is to develop the criteria which will indicate the most important defects which account for the anergic state in individual patients. One such approach would be to develop a multiple linear regression such as the following:

Probability of decreased host resistance

$$
\begin{aligned}
= \; & A + B\,(\text{immunodeficiency}) + C\,(\text{malnutrition}) \\
& + D\,(\text{blood volume}) + E\,(\text{trauma}) \\
& + F\,(\text{surgery}) + H\,(\text{age}) \\
& + G\,(\text{cancer}) + I\,(?)\ldots
\end{aligned}
$$

In this way the therapeutic approach to patients may be individualized and optimum results achieved.

ADDENDUM

The above approach has been effectively used by Buzby, G. P., Mullen, J. L., Matthews, D. C., et al. Prognostic Nutritional Index in Gastrointestinal Surgery. Am. J. Surg. in press 1979.

Acknowledgments

Our thanks to Mrs. Dianne Gotto for all aspects of the study, Ms. Irene Hughes for technical assistance and Miss Gina Eustace for secretarial assistance.

References

1. Bistrian, B. R., Blackburn, G. L., Schrimshaw, N. S. et al.: Cellular Immunity in Semistarved States in Hosptialized Adults. Am. J. Clin. Nut., 28:1148, 1975.
2. Blackburn, G. L., Bistrian, B. R., Miani, B. S. et al.: Nutritional and Metabolic Assessment of the Hospitalized Patient. J. Parenteral Enteral Nut., 1:11, 1977.
3. Boyden, S.: Chemotactic Effect of Antibody and Antigen. J. Exp. Med., 115:453, 1962.
4. Brugmans, J., Schuermans, V., De Cock, W. et al.: Restoration of Host Defense Mechanisms in Man by Levamisole. Life Sci., 13:1499, 1973.
5. Christou, N. V. and Meakins, J. L.: Neutrophil Function in Surgical Patients: In Vitro Correction of Abnormal Neutrophil Chemotaxis by Levamisole. Surgery, 85:543, 1979.
6. Christou, N. V. and Meakins, J. L.: Neutrophil Function in Surgical Patients: Two Inhibitors of Granulocyte Chemotaxis Associated with Sepsis. J. Surg. Res., 26:355, 1979.
7. Copeland, E. M., MacFadyen, B. V. and Dudrick, S. J.: Effect of Intravenous Hyperalimentation on Established Delayed Hypersensitivity in the Cancer Patient. Ann. Surg., 184:60, 1976.
8. De Cree, J., Verhaegen, H., De Cock, W. et al.: Impaired Neutrophil Phagocytosis. Lancet, II:294, 1974.
9. Eilber, F. R. and Morton, D. L.: Impaired Immunologic Reactivity and Recurrence Following Cancer Surgery. Cancer, 24:362, 1970.
10. George, C., Robin, M., Carlet, J. et al.: Tests Cutanés Explorant l'Immunité Cellulaire Chez les Malades en Reanimation. Nouv. Presse Méd., 7:2541, 1978.
11. Hoebeke, J. and Franchi, G.: Influence of Tetramisole and Its Optical isomers on the Mononuclear Phagocytic System: Effect on Carbon Clearance in Mice. J. Reticuloendothel. Soc., 14:317, 1973.
12. Johnson, W. C., Ulrich, F., Meguid, M. M. et al.: Role of Delayed Hypersensitivity in Predicting Prostoperative Morbidity and Mortality. Am. J. Surg., 137:536, 1979.
13. Lewis, R. T. and Klein, H.: Risk Factors in Postoperative Sepsis: Significance of Preoperative Lymphocytopenia. J. Surg. Res. 26:365, 1979.
14. MacLean, L. D., Goldstein, M., MacDonald, J. E. et al.: Results of Cholecystectomy in 1000 Consecutive Patients. Can. J. Surg., 18:459, 1975.
15. MacLean, L. D., Meakins, J. L., Taguchi, K. et al.: Host resistance in Sepsis and Trauma. Ann. Surg., 182:207, 1975.
16. Meakins, J. L., McLean, A. P. H., Kelly, R. et al.: Delayed Hypersensitivity and Neutrophil Chemotaxis: Effect of Trauma. J. Trauma, 18:240, 1978.
17. Meakins, J. L., Pietsch, J. B., Bubenik, O. et al.: Delayed Hypersensitivity: Indicator of Acquired Failure of Host Defenses in Sepsis and Trauma. Ann. Surg., 186:241, 1977.
18. Pietsch, J. B., Meakins, J. L. and MacLean, L. D.: Delayed Hypersensitivity Response: Application in Clinical Surgery. Surgery, 82:349, 1977.
19. Renoux, G. and Renoux, M.: Effect Immunostimulant d'un Imidothiazole dans l'Immunisation des Souris Contre l'Infection par *Brucella abortus*. C.R. Acad. Sci. 272:349, 1971.
20. Renoux, G., Renoux, M. and Morand, P. H.: Action Immunostimulante du Levamisole sur les Personnes Agées. Rev. Méd. Tour, 7:797, 1973.
21. Spanier, A. H., Pietsch, J. B., Meakins, J. L. et al.: The Relationship Between Immune Competence and Nutrition. Surg. Forum 27:332, 1976.
22. Tripodi, D., Parks, L. D. and Brugmans, J.: Drug-induced Restoration of Cutaneous Delayed Hypersensitivity in Anergic Patients with Cancer. N. Engl. J. Med., 289:354, 1973.
23. Van Ginckel, R. F. and Hoebeke, J.: Carbon Clearance Enhancing Factor in Serum from Levamisole Treated Mice. J. Reticuloendothel. Soc., 17:65, 1975.
24. Zigmond, S. H. and Hirsch, J. G.: Leukocyte Locomotion and Chemotaxis. J. Exp. Med., 137:387, 1973.

DISCUSSION

DR. WILLIAM STAHL, JR. (New York, New York): I would like to compliment Dr. Meakins and Dr. MacLean's group for again bringing to our attention the vital importance of the immune system, as they have over the last few years. This is a new area for surgeons to become interested in after being stimulated by them. I would point out that the skin test is an important measure, but immune competence is a much more complicated phenomenon than the skin test alone can indicate.

In the Shock/Trauma Unit at Metropolitan Hospital Center we have been looking at many parameters of the immune system. The work has been done in collaboration with Sloan-Kettering Institute for Cancer Research, specifically with Drs. Robert Good, Charlotte Cunningham-Rundles and Norbibi Day.

(slide) This shows the measurements that we are doing: skin tests, lymphocyte surface markers and lymphocyte functions, antigen and mitogen stimulation, all of the immunoglobulins and certain fractions of complement. To summarize our first 25 seriously traumatized or septic patients, we have shown, as many others have, that the immunoglobulins in the blood stay at quite normal levels, even when patients are severely ill. This may be due to the fact that these proteins persist over a period of time, and it may take time to develop deficiencies.

Lymphocyte function stayed surprisingly good, and we do believe as well will hear, I think, in the next paper, that there is some depressant serum factor which is present, but that the cells remain normally reactive for a long time.

Our skin test data showed that in this seriously ill group of 25 patients, ten patients were anergic and 15 patients were reactive. The 15 reactive patients all survived, six of the anergic patients survived, and four died. The anergic group, therefore, is a mixed group of patients, some of whom will stand operation, trauma and sepsis quite well, and others will not. Our preliminary studies have shown some factors to be correlated with the demise of these patients. The surface marker data show that, except for T-rosettes, all the other data are nondiscriminatory. We do not know quite what that means, but the T-cell populations are specifically reduced in the patients who die, as opposed to the patients who live. Whether this means that there are fewer T-cells, or that something is altering the surface membrane markers, we are not sure.

In addition, we found that complement—total hemolytic complement, and C-3—is specifically reduced in the patients who die, as opposed to the patients who live. As has previously been known, some patients who survive severe sepsis actually show a tremendous rise in complement.

Thus in our study we have learned that we can take patients who are anergic to skin tests and, by doing T-cell and complement levels, pick out of those patients a group of patients who will do much better than one would think, just by looking at their anergic state. In fact, we have used the T-cell levels and complement levels to assure us that we can go ahead and operate on patients who are nonreactive to skin tests.

The important thing is that these two tests are quite simple to do, can be done overnight or in a period of a few hours and perhaps will be able to separate anergic patients into those who are really at high risk and those who can withstand future trauma or operation.

DR. BASIL A. PRUITT, JR. (Fort Sam Houston, Texas): In our laboratory we have identified suppressed glucose oxidation by both the hexose monophosphate shunt pathway and by glycolysis in stimulated and unstimulated neutrophils from patients with burns. The changes appear to be related to increased catecholamine excretion and may be the mechanism by which neutrophil function is imparied.

I wonder, Dr. Meakins, whether your anergic patients, as opposed to the reactive patients, had any significant increases in their catecholamine levels.

DR. THOMAS K. HUNT (San Francisco): I would like to come to Dr. Meakins's aid because he hasn't time in ten minutes to explain that a skin test is a phenomenon whose components are not fully known and are undoubtedly many. First, the antigen has to be recognized; healthy cells have to sense the chemoreactant, must migrate to the site, must produce signals for further cells to migrate, must perform their functions and so forth. The skin test also fails to measure several important effects, particularly the ability of polymorphonuclear leukocytes to phagocytose and kill bacteria once they have encountered them.

Dr. Meakins's audiences tend to oversimplify his results and try to give them a single explanation. In his hands results tend to correlate rather closely with chemotaxis, but undoubtedly not exclusively. Others have found other factors. Dr. Stahl has shown rather nicely that there are a wide variety of explanations for the findings of the Montreal group. The beauty of the skin tests, in fact, lies in the fact that they are so nonspecific. They are so widely inclusive of immune phenomena that they have a clinical predictiveness, whereas the more sophisticated tests, which better measure one or another immune mechanisms, are not so clinically useful.

DR. DONALD L. MORTON (Los Angeles, California): This is an interesting paper. However, the authors have grouped patients who have anergy from cancer together with those who have anergy from sepsis; the mechanisms of anergy may be different for these two conditions. It is clear in patients who have anergy from cancer that the anergy is related to tumor burden—successful resection of the tumor can result in improved immune competence and loss of anergy. This, in fact, may occur in sepsis, but I would like to see the authors' data divided between those patients who have anergy from cancer and those who have it from sepsis. Are the differences still statistically significant?

Second, I would like to make the observation that 60% of the patients who received placebo had improvement in their skin test reactivity and in some of their other immune parameters. We have observed a similar effect on anergy in cancer patients with placebo vs. levamisole. The mechanism for the placebo effect is unknown. It could be that the repeated skin tests induce a secondary response, or that the placebo may affect some central mechanism; nonetheless, it is something that really has to be carefully controlled for in all immunorestorative studies.

DR. J. L. MEAKINS (Closing discussion): Dr. Stahl, the one thing we noticed that is missing from the battery of immunologic studies that you are looking at is studies of neutrophil function. We do not think that the skin tests are a true reflection in these patients of cell-mediated immunity. We have attempted in the past to show that blastogenic responses of lymphocytes to the mitogens, pokeweed and PHA, and in mixed lymphocyte culture, the generation of blastogenic factor, production of cell-mediated lympholysis, and so on, was abnormal, and have never been able to do so. T-lymphocyte rosetting is reduced in anergic patients and appears to be mediated by a serum factor. The other cell function that we found specifically abnormal was that with regard to neutrophils.

Dr. Hunt has responded in many respects as I would in response to your comments. This is an extremely complicated problem, and it is unlikely that these problems can be tied together in a single package.

We have done no studies, Dr. Pruitt, with regard to glucose utilization in neutrophils in any of these patients.

I can only thank Dr. Hunt for his comment. He has enunciated much of what I would have liked to have said.

Dr. Morton, we have gotten together our patients with regard to cancer, and that material is submitted. Our present data do not show that there is an increased incidence of anergy in the global population of patients with cancer in the hospital. We have been unable to relate anergy to tumor load in our specific population, only to the secondary, *i.e.*, nutritional, effects of the neoplasm. It may be that we are not looking at this issue in the same way.

We do agree that there is a difference in the etiology of anergy explaining in part why different patient populations are anergic, although in likelihood there will be a synthetic approach to immune regulation that will allow an explanation of this.

The study on levamisole is clearly a preliminary one, and it is not wholly satisfactory, as is explained in the manuscript. In the 60% of patients whose skin tests improved, we feel that surgical treatment and correction of their underlying illness played a major role here. Data not presented on the retrospective group show that in those patients whose skin tests improved, in whom we did preoperative and postoperative chemotaxis, there is a statistical improvement in their chemotaxis as a result solely of the operation.

In summary, this is a very complicated problem, and I do not think we are going to be able to solve it in any way with a single hypothesis, although in all likelihood these multiple features are mediated by a final common mechanism.

Correlation Between Anergy and a Circulating Immunosuppressive Factor Following Major Surgical Trauma

GERARD A. McLOUGHLIN, M.D., ANDREW V. WU, M.D., INNA SAPOROSCHETZ, A.B.,
RICHARD NIMBERG, D.M.D., PH.D., JOHN A. MANNICK, M.D.

In order to clarify the relationship between anergy and immunosuppressive activity in the serum, we studied 46 previously well patients before and at three, five, seven and 28 days after surgery. Delayed hypersensitivity was measured by skin testing with four common recall antigens, and serum immunosuppressive activity was determined by the ability of the patient's serum in 10% concentration to suppress by 50% or more the phytohemagglutinin (PHA) stimulation of normal human lymphocytes as compared to pooled normal serum. Prior to surgery, all patients manifested delayed hypersensitivity to one or more antigens, and no patient had immunosuppressive serum. Fifteen patients underwent minor surgery under general anesthesia and did not develop anergy or immunosuppressive serum. Thirty-one patients underwent major cardiovascular surgery. Thirteen of these patients became anergic by day 3 after operation, and 11 of the 13 developed immunosuppressive serum. Eighteen patients maintained delayed hypersensitivity after major surgery, and only three developed immunosuppressive serum. The correlation between anergy and immunosuppressive serum was highly significant ($p < 0.001$). There was a significant difference in the degree of suppressive activity in the serum of the anergic and reactive patient groups for each postoperative day studied until day 28, when there was recovery of delayed hypersensitivity and lack of immunosuppressive serum. The occurrence of postoperative anergy and immunosuppressive serum was not related to the patient's age, sex, number of perioperative blood transfusions or duration of anesthesia but was associated with an increase in postoperative infectious complications ($p < 0.05$) and in postoperative days in the hospital ($p < 0.01$). Pooled immunosuppressive serum from anergic patients was fractionated by ion exchange chromatography, gel filtration and preparative high voltage electrophoresis. The majority of the immunosuppressive activity could be accounted for by an electrophoretically homogenous polypeptide-containing fraction not identified in the serum of patients undergoing minor surgery or in normal individuals. We conclude that anergy occurring after major operative trauma is associated with the appearance of a circulating immunosuppressive molecular species and that these events are in turn associated with increased patient morbidity and increased length of hospitalization.

From the Department of Surgery,
Peter Bent Brigham Hospital and Harvard Medical School,
and the Department of Biochemistry,
Boston University School of Medicine,
Boston, Massachusetts

ANERGY IS FOUND in surgical patients with nutritional deprivation or advanced malignancy and is associated with an increased incidence of sepsis and mortality.[3-6,8] Since restoration of delayed hypersensitivity responsiveness has been reported in such patients following parenteral hyperalimentation,[3,9] this suggests an underlying mechanism for the anergy observed in these depleted individuals. On the other hand, there are conflicting reports as to whether or not major surgical trauma in nondepleted patients is followed by anergy.[8,10] Moreover, if anergy does occur under these circumstances, it is not clear what the mechanism is and what effect, if any, the anergic state has on patient morbidity and mortality. A good deal of recent investigative work has focused on defects in polymorphonuclear leukocyte function detected in anergic surgical patients.[1,4,6] While polymorphonuclear leukocytes clearly play an important role in the defense against bacterial infection in man, they have not been shown to be obligatory participants in delayed hypersensitivity responses.[11] These responses are mediated by specifically sensitized T lymphocytes, which in turn elicit the nonspecific cooperation of macrophages.

We have recently reported that major operative trauma is often followed by the appearance in the serum of a circulating factor or factors suppressive of T-lymphocyte activation.[2] We therefore undertook the present investigation in a group of well-nourished

---

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

Reprint requests: John A. Mannick, M.D., 721 Huntington Avenue, Boston, Massachusetts 02115.

Supported in part by Army contract #DAMD17-76-C-6076 and NIH research grant GM26016-01.

0003-4932/79/0900/0297 $00.90 © J. B. Lippincott Company

TABLE 1. *Skin Test: Delayed Hypersensitivity Response to Four Recall Antigens (Mumps, SK-SD, PPD, Candida)*

	Grade	Response (Diameter of Induration)
Anergic	0	0
	1	<3 mm for 1
Reactive	2	>5 mm for 1 or >3 mm for 2
	3	>10 mm for 1 or >10 mm for 1 and >5 mm for another
	4	>20 mm for 1 or >15 for 1 with 10 mm for another or >10 mm for 2 or more

surgical patients, none of whom had malignancy, to determine whether or not the appearance of circulating immunosuppressive factors in the serum postoperatively was associated with the manifestation of anergy and whether the anergic state was in turn associated with an altered patient prognosis. We were also concerned with the purification and characterization of the immunosuppressive substance or substances detected in the serum of these surgically traumatized patients.

Patient Population and Methods

Forty-six patients were studied. Fifteen of these patients received general anesthesia for minor surgical operations. Seven underwent inguinal hernia repair, two had dilatation and curettage, three had multiple dental extractions, and three had orthopedic manipulations. The age of this patient population ranged from 35 to 75 years, with a mean age of 56 years. There were 13 males and two females.

Thirty-one patients underwent major cardiovascular surgery under general anesthesia. Sixteen of these patients had abdominal aortic aneurysm resections. Ten underwent coronary artery bypass grafts, and five underwent aortic or mitral valve replacement, with or without coronary artery bypass grafting. The age of this patient group ranged from 42 to 75 years. The mean age was 62 years. There were 27 males and four females. No patient judged clinically to be nutritionally depleted was included in this study, and no patient had cancer. In addition, nine healthy normal volunteers, ranging in age from 24 to 63 years, were used as control serum donors in some of the studies. Informed consent was obtained from all patients before studies were initiated.

All patients were skin tested with four recall antigens for delayed hypersensitivity responsiveness 2 days prior to surgery. The antigens were mumps skin test antigen (Eli Lilly & Co., Indianapolis, IN), 0.1 ml; 50 units of streptokinase-streptodornase (SK-SD) (Lederle Laboratories, Pearl River, NY); intermediate strength tuberculin purified protein derivative (PPD) (Merck, Sharp and Dohme, West Point, PA), 0.1 ml; and *Candida* skin test antigen (Greer Laboratories, New York, NY), 0.1 ml. All skin tests were read at 24 and 48 hours and were scored according to the system listed in Table 1. Responses were graded by the diameter of the area of induration. Patients were considered to be anergic if they had responses of grades 0 and 1 and reactive if they had responses of grades 2, 3 and 4. No patient who was anergic preoperatively was included in these investigations. Skin tests were repeated in all patients on the second postoperative day, the seventh postoperative day and the twenty-eighth postoperative day.

Histamine (Eli Lilly), 0.5 mg, was injected intradermally as a control for an intact inflammatory response in the postoperative period. Thirty-milliliter venous blood samples were drawn beginning 2 days preoperatively and then on the third postoperative day, the fifth postoperative day, the seventh postoperative day, the fourteenth postoperative day (in some patients) and on the twenty-eighth postoperative day. In order to obtain serum samples, the blood was allowed to clot and retract, and the serum was removed by centrifugation at 2000 × g for 30 min and stored in the cold.

In Vitro *Assay of Immunosuppressive Activity*

Serum samples were tested for immunosuppressive activity *in vitro* by studying their ability to inhibit phytohemagglutinin (PHA)-induced normal human lymphocyte proliferation. Heparinized venous blood was obtained from the normal donors, and after gravity sedimentation of the erythrocytes for 2 hours at 20°, the serum layer was placed on sterile nylon wool columns and eluted with Eagle's minimal essential medium (MEM). After washing in MEM, the cells were counted and tested for viability by trypan blue dye exclusion. The procedure yielded a preparation of small lymphocytes, 95% or more pure and 95% or more viable. The micro method was used for testing lymphocyte stimulation. In the wells of Microtest® plates (Falcon Plastics) 2.5×10^5 lymphocytes were placed in 0.2 ml of MEM containing 1% glutamine, 5% fetal calf serum, 100 units of penicillin and 100 μg of streptomycin per milliliter and a range of stimulatory doses of purified PHA (2.5, 5 and 10 μg/ml). Serums to be tested for immunosuppressive activity were added to the culture medium in 10% concentration. Controls included cultures with no additions and those with 10% pooled normal serum. The same normal serum pool was used for all experiments. Microtest plates were then incubated in a 5% CO_2 water-saturated environment at 37° for 48 hours. ^{3}H-thymidine, 1 μCi, was then added to each well. The cultures were processed 16–18 hours later by a Mash II® microharvester (Microbiological Associates) and counted in a Packard liquid scintillation counter. All determinations were performed in triplicate. Some wells in each experiment were used for a trypan blue viability determination of the cells incubated with or without the serums being tested. No cytotoxic serums were found in these experiments. Immunosuppression *in vitro* was calculated by the formula

$$\%\ \text{Suppression} = 1 - \frac{\text{CPM, experimental wells with PHA} - \text{CPM of control wells without PHA}}{\text{CPM of control wells with PHA} - \text{CPM of control wells without PHA}} \times 100$$

In these studies, suppression of PHA stimulation by experimental serum of 50% or more when compared with control serum was considered significant.

Isolation of Suppressive Material from the Serum

Ten-milliliter samples of serum were fractionated by diethylaminoethyl (DEAE) cellulose ion exchange chromatography in 0.005 M acetate buffer (pH 5.0). The protein peaks from this separation were then recovered by lyophilization and tested for immunosuppressive activity in tissue culture as described above. Lyophilized protein, 100 mg, was then dissolved in distilled water and placed on a G-25 Sephadex® column. The protein peaks from this column were then similarly recovered by lyophilization. After testing for immunosuppressive activity *in vitro*, the G-25 fractions were dissolved in distilled water and acetic acid, pH 3.5, and placed in 10–20-mg aliquots on paper strips for high voltage electrophoresis along with reference amino acids. A portion of the electrophoresis strip was stained with ninhydrin, and the remainder of the strip was cut into fractions containing the various ninhydrin staining moieties. The fractions were then eluted from the paper with distilled water-acetic acid solution and recovered by lyophilization. Each of the recovered, presumably peptide-containing moieties was then tested for suppressive activity in tissue culture.

In Vivo *Assay of Immunosuppressive Activity*

To confirm the results of the *in vitro* tissue culture assay, suppressive and nonsuppressive fractions obtained by G-25 gel filtration were tested for immunosuppressive activity *in vivo* in mice by the Jerne hemolytic plaque assay. Adult C3H mice (Jackson Laboratories) were injected intraperitoneally with test or control fractions 24 hours before the intraperitoneal injection of 4 × 10^8 sheep erythrocytes. Four days later their spleens were harvested, and the numbers of plaque-forming cells were enumerated as described previously.[7] Duplicate determinations were performed in each of five animals per experimental group.

Cortisol Determinations

Serum cortisol determinations were performed in the hospital laboratory by the competitive protein-binding method.

Results

Correlation of Anergy with Suppressive Activity in the Serum

Of the 15 patients undergoing minor surgical procedures under general anesthesia, no patient became anergic at any time in the postoperative period and no patient developed immunosuppressive serum as determined by the ability of the serum in 10% concentration to suppress by 50% or more the PHA stimulation of normal human lymphocytes (Table 2). However, of the 31 patients who underwent major cardiovascular surgery, 13 became anergic to the skin test antigens by postoperative day 3, and of these 13 patients, 11 developed immunosuppressive serum. Of the 18 patients who remained reactive to the skin test antigens, only three developed immunosuppressive serum at any time in the postoperative period. By χ^2 analysis the correlation between immunosuppressive serum and anergy in the patients undergoing major cardiovascular surgery is highly significant ($p < 0.001$).

As shown in Figure 1, the suppressive activity in the serum of the entire group of patients who became anergic in the postoperative period was significantly

TABLE 2. *Correlation of Anergy with Suppressive Serum Three Days After Surgical Trauma*

Surgery	Skin Test	Immunosuppressive Serum*	Nonsuppressive Serum	Total No.
Minor	Positive	0	15	15
	Negative	0	0	0
Major	Positive	3	15	18
	Negative	11†	2	13

* Immunosuppressive serum at 10% concentration was more than 50% suppressive of PHA stimulation of normal human lymphocytes.
† Chi square with Yate's correction: *p < 0.001.

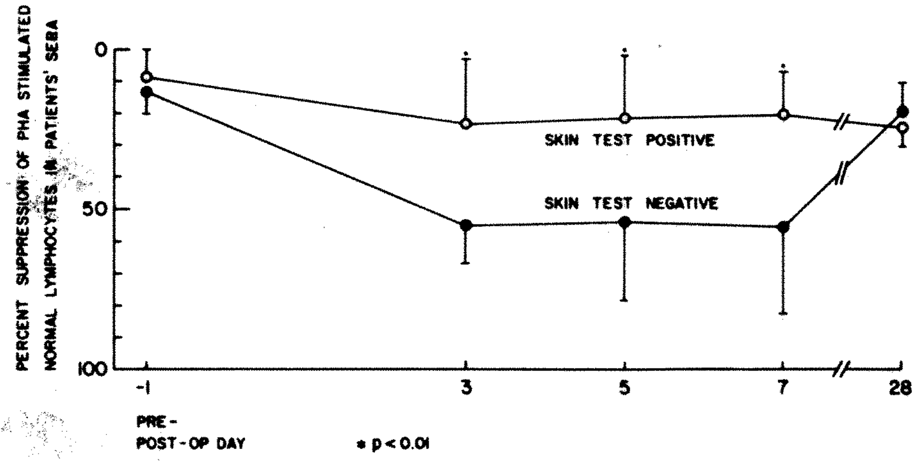


FIG. 1. The immunosuppressive activity in the serum of negative skin test and positive skin test patients following major cardiovascular surgery in the present study. Results are presented as mean percentage suppression of PHA stimulation of normal peripheral blood lymphocytes (±S.D.) by test serum in 10% concentration. The two groups differ significantly on postoperative days 3, 5 and 7 as determined by the paired t-test ($p < 0.001$).

greater than that in the serum of patients who remained reactive to the skin test antigens for the first 7 days postoperatively. By day 28 when the patients were seen as outpatients, significant suppressive activity in the serum had disappeared. By day 28 the patients had also regained responsiveness to the skin test antigens. All patients responded normally to intradermal histamine in the early postoperative period. Serum cortisol levels were within the normal range in pooled and selected individual postoperative samples.

Association of Anergy and Immunosuppressive Serum with Patient Morbidity

As noted in Table 3, 11 of the patients undergoing major surgery developed both anergy and immunosuppressive serum in the postoperative period, while 15 manifested neither. The two groups did not differ significantly from one another in age or sex. They also did not differ from one another with respect to the number of perioperative blood transfusions received or the duration of anesthesia. However, the patients with anergy and suppressive serum developed significantly more infectious complications that required antibiotic therapy in the postoperative period. These were predominantly pulmonary and urinary tract infections. Also the group of patients with anergy and suppressive serum spent significantly more days in the hospital postoperatively.

Isolation of Suppressive Material from the Serum

Pooled immunosuppressive serum from eight of the patients undergoing major surgery who developed anergy and suppressive serum in the postoperative period was subjected to DEAE cellulose ion exchange chromatography. The peaks obtained were tested for immunosuppressive activity at 5, 2 and 1 mg/ml. Controls included pooled serum from eight patients who underwent minor surgical procedures and pooled serum from eight normal individuals. Suppressive activity from the immunosuppressive serum from patients in the major surgical group was found principally in the first two peaks from the DEAE column.

These suppressive peaks from DEAE chromatography were then subjected to gel filtration on a G-25

TABLE 3. *Major Surgical Patients*

Anergy and Suppressive Serum	Blood Transfusions	Duration of Anesthesia (hr)	Postop. Infectious Complications	Postop. Days in Hospital
Yes n = 11, M = 10, F = 1, av. age = 63	2.33 ± 0.89*	4.02 ± 0.31*	6/11 $p < 0.05$	13.5 ± 4.2* $p < 0.01$
No n = 15, M = 13, F = 2, av. age = 62	2.33 ± 0.87	4.11 ± 0.24	1/15	8.8 ± 2.2

* Mean ± S.D.

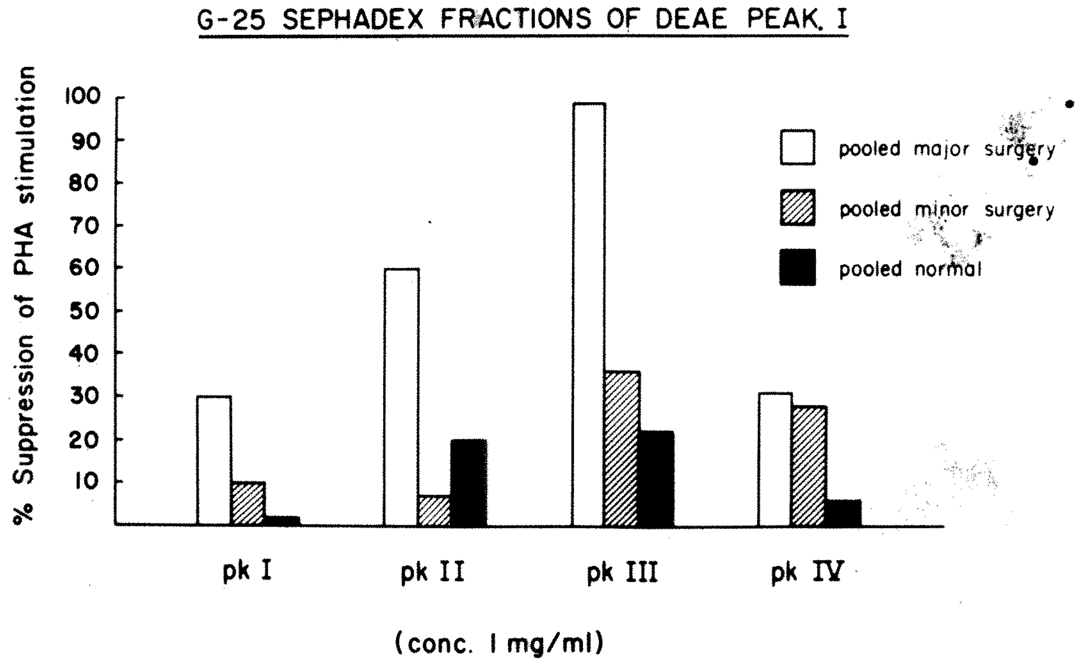


FIG. 2. Suppressive activity of fractions of serum obtained by G-25 Sephadex chromatography and tested at 1 mg/ml concentration. Results are presented as mean percentage suppression of PHA stimulation of normal human lymphocytes. It is apparent that the suppressive activity in the serum of patients following major cardiovascular surgery is found chiefly in peak 3. Pooled serum from patients undergoing minor surgery or from normal individuals contains little suppressive activity.

Sephadex column, and the resultant polypeptide peaks were lyophilized and tested for immunosuppressive activity in tissue culture at concentrations of 2, 1 and 0.5 mg/ml. As noted in Figure 2, the immunosuppressive activity in the serum from suppressed major surgical patients was located principally in peak 3 from the G-25 column. Very little suppressive activity was recovered from serum from patients subjected to minor surgery or from normal individuals.

G-25 peak 3 from suppressed patients undergoing major surgery was also tested for immunosuppressive activity in the mouse. It is apparent from Table 4 that G-25 peak 3 at a dose of 5 mg per mouse produced very significant suppression of the plaque-forming cell response to sheep erythrocytes in contrast to G-25 peak 1. At this dosage the concentration of G-25 peak 3 in mouse serum was calculated to be approximately the same as in the serum of suppressed major surgical patients.

Finally, G-25 peak 3 from suppressed patients undergoing major surgery was further fractionated by preparative high voltage electrophoresis. It was found that the immunosuppressive activity was recovered principally in a highly basic fraction, fraction 11 (Table 5). Fraction 11 was not detectable in the serum of patients who had undergone minor surgery or in the serum of normal individuals. The same area in the electrophoresis strip contained negligible immunosuppressive activity in these control groups.

Fraction 11 from suppressed major surgical patients was subjected to acid hydrolysis and yielded amino acids plus a so far unidentified ninhydrin staining basic component, more basic than known amino acids but less basic than known polyamines.

Discussion

These results clearly demonstrate that following major cardiovascular surgery, temporary anergy fre-

TABLE 4. *Effect of Major Surgery Serum Fractions on Direct Plaque-Forming Cell Response to SRBC in C3H Mice*

Treatment	Plaques per 10^6 Spleen Cells (±S.D.)	Per Cent Suppression
None	485 ± 7.7	
G-25 peak I		
5 mg	502 ± 22.4	0
1 mg	464 ± 6.1	4
G-25 peak 3		
5 mg	212 ± 12.1	57
1 mg	466 ± 15.6	4

TABLE 5. *Serum Fractionation: High Voltage Electrophoresis of G-25 Sephadex Peak 3 (% Suppression of PHA Stimulation at 1–2 μg/ml)*

	Fraction												
	⊕	1	2	3	4	5	6	7	8	9	10	11	⊖
Major surgery		14	12		24		17	21	0	24		63	
Minor surgery		0	13	0		5	12	11	13	3	0	10	
Normal		0	0	9	0	5	35	13	7	8	37	0	

quently appears in apparently well-nourished patients who do not have malignancy. Our results do not agree entirely with those reported by Slade et al.,[10] who found that patients undergoing major surgery consistently show decreased delayed hypersensitivity responses postoperatively, and our findings are also clearly at variance with those of Pietsch et al.[8] who concluded that skin test responses were not altered by major surgery in apparently nondepleted patients. The reasons for these discrepancies are not entirely clear, but the magnitude of the operative trauma may well be related to the incidence of postoperative anergy in a well-nourished patient population.

Anergy in the patients in the present study was accompanied by the appearance of circulating immunosuppressive activity in the serum, which blocked the activation of T lymphocytes from normal individuals but was not cytotoxic to these cells. The appearance of anergy and immunosuppressive activity in the serum was not the direct result of general anesthesia, since a group of 15 patients undergoing minor surgery under general anesthesia developed neither anergy nor immunosuppressive serum in the postoperative period. Among the patients undergoing major cardiovascular surgery, those who developed anergy and immunosuppressive serum could not be distinguished from those who did not on the basis of age, sex, number of perioperative blood transfusions or duration of anesthesia. However, patients with anergy and immunosuppressive serum had significantly more infectious complications requiring antibiotic therapy in the postoperative period than those patients who remained responsive to recall antigens and did not develop immunosuppressive serum. While there were no postoperative deaths, patients with anergy and immunosuppressive serum also spent significantly more days in the hospital postoperatively than patients who remained responsive.

The mechanism underlying the appearance of anergy and immunosuppressive serum in some of the patients undergoing major cardiovascular surgery in the present study remains obscure. Anergy in these patients cannot be explained on the basis of a generalized incapacity to mount an inflammatory response, since all patients responded normally to intradermal histamine. None of the patients was apparently nutritionally depleted, and no patient had a known malignancy. We have previously demonstrated that immunosuppressive serum in surgical patients is not related to serum cortisol concentrations,[2] and serum cortisol determinations in the patients reported here showed normal levels postoperatively. The most obvious explanation for the present observations appears to be that major operative trauma in itself triggers a temporary inhibition of cellular immunity, possibly mediated by circulating immunosuppressive factors.

The present results also shed some light on the nature of the immunosuppressive activity in the serum of the patients who became anergic after major surgery. In these individuals the majority but not all of the immunosuppressive activity can be accounted for by a polypeptide-like fraction which from its behavior on gel filtration has a molecular weight of approximately 1000 daltons. This material can be recovered as a homogeneous molecular species by high voltage electrophoresis. The highly basic character of this material on electrophoresis makes it unlikely that it is a conventional polypeptide; however, it is not as basic as any of the known polyamines. This material was not recoverable in detectable quantities by identical fractionation of the serum from normal individuals or from patients who had undergone minor surgical procedures.

It is tempting to speculate that the appearance of an immunosuppressive molecular species in the serum of patients following major surgical trauma may be the cause of the anergy seen in these individuals, since there is a statistically significant association between these phenomena. The fact that the gel filtration fraction in which the patients' serum suppressive activity was concentrated also suppressed the ability of mice to mount an antibody response to a T-cell dependent antigen adds weight to this hypothesis. However, a causal relationship between this suppressive substance and clinical anergy cannot yet be claimed to be established.

References

1. Alexander, J. W., Ogle, C. K., Stinnett, J. D. and MacMillan, B. G.: A Sequential, Prospective Analysis of Immunologic Abnormalities and Infection Following Severe Thermal Injury. Ann. Surg., 188:6, 1978.
2. Constantian, M. B., Menzoian, J. O., Nimberg, R. B. et al.: Association of a Circulating Immunosuppressive Polypeptide with Operative and Accidental Trauma. Ann. Surg., 186:1, 1977.
3. Copeland, E. M., MacFadyen, B. V. and Dudrick, S. J.: Effect of Intravenous Hyperalimentation on Established Delayed Hypersensitivity in the Cancer Patient. Ann. Surg., 184:60, 1976.
4. Johnson, W. C., Ulrich, F., Meguid, M. M. et al.: Role of Delayed Hypersensitivity in Predicting Postoperative Morbidity and Mortality. Am. J. Surg. 137:536–542, 1979.
5. Law, D. K., Dudrick, S. J. and Abdou, N. I.: The Effect of Protein Calorie Malnutrition on Immune Competence of the Surgical Patient. Surg. Gynecol. Obstet., 139:257, 1974.
6. Meakins, J. L., Pietsch, J. B., Bubenick, O. et al.: Delayed Hypersensitivity: Indicator of Acquired Failure of Host Defenses in Sepsis and Trauma. Ann. Surg., 186:3, 1977.
7. Occhino, J., Glasgow, A. H., Cooperband, S. R. et al.: Isolation of an Immunosuppressive Peptide Fraction from Human Plasma. J. Immunol., 110:685, 1975.

8. Pietsch, J. B., Meakins, J. L., Gotto, D. and MacLean, L. D.: Delayed Hypersensitivity Responses: The Effect of Surgery. J. Surg. Res., 22:228–230, 1977.
9. Pietsch, J. B., Meakins, J. L. and MacLean, L. D.: The Delayed Hypersensitivity Response: Application in Clinical Surgery. Surgery, 82:349–355, 1977.
10. Slade, M. S., Simmons, R. L., Yunis, E. and Greenberg, L. J.: Immunodepression After Major Surgery in Normal Patients. Surgery, 78:363–372, 1975.
11. Waksman, B. H.: Cellular Hypersensitivity and Immunity: Conceptual Changes in Last Decade. (Commentary) Cell. Immunol., 42:155–169, 1979.

DISCUSSION

DR. GEORGE H. A. CLOWES, JR. (Boston, Massachusetts): Specifically in relation to John Mannick's paper, the more I look at trauma and sepsis, the more I realize that they have the same effects metabolically, and in a variety of other ways physiologically. That is, if we assume that the trauma patient has gone beyond the shock phase. The response is very similar then to that of the septic patient.

For some time we have been interested in circulating factors of the small nonprotein peptide type that Dr. Mannick has discussed. (slide) This is a thin-layer chromatograph with a ninhydrin stain that shows in that fraction around 3000–5000 molecular weight a great difference between normal plasma and septic plasma.

Here is what is found when that same fraction from 1000 to 10,000 molecular weight is examined by column chromatography. The point is that the 206 nanometer light exposure, which activates the peptide bonds, demonstrates two large peaks in the fraction from a septic or traumatized patient that are just barely discernible in the plasma fraction from a normal person. This demonstrates that there are many peptide substances circulating under these conditions that are not present in the normal individual.

(slide) It is possible to show a remarkable correlation of the presence of these substances with the clinical state. If one binds these peptides to Sephadex, it is possible to make an antibody. We see here reactions in a series of septic patients, which are absent in the normal person when this immunologic diffusion test is done.

(slide) What is the significance of this? This slide emphasizes the importance of how these agents affect the metabolism of incubated muscle cells. We see virtually no change in the metabolism when saline solution is added. There is a response to insulin in terms of CO_2 production. If normal human plasma or normal plasma fraction are added we get the same response, but if we add the septic plasma, or the septic fraction, we get a suppression of insulin response. That is just one metabolic phenomenon. I can tell you from experience that the same thing happens for protein synthesis and a variety of other parameters which we have measured.

What I'm really saying is that, to me, the bottom line of all this work, and the important response in which we are interested is protein synthesis. After all, T-cell function depends on its ability to make a protein pretty quickly, and I would say that this probably is the common denominator in all of these reactions. The same agent that Dr. Mannick has so elegantly demonstrated to you this morning as well as many other peptides are probably at work in the other phenomena the other two speakers described this morning.

DR. JONATHAN L. MEAKINS (Montreal, Quebec): Dr. Mannick's paper is a very exciting one, and approaches the problems of immune regulation in a normal, well-nourished population. We have approached this from a slightly different point of view, in terms of decreased host resistance to infection and immunoregulation.

(slide) Dr. Christou recently presented this information on the effect of anergic patients' serum on neutrophil and lymphocyte chemotaxis. The test cells are normal, and it is apparent that relatively anergic and anergic serum reduces PMN chemotaxis and lymphocyte chemotaxis to the anergic range.

(slide) Trauma patients, studied in the emergency department as they are admitted to the hospital, are seen to have abnormal chemotaxis 2–12 hours after injury. Anergy subsequently developed in all of them. This abnormality of their chemotaxis must surely be mediated by a serum factor to appear so promptly.

(slide) We have looked at the concentration of anergic serums required to inhibit chemotaxis and find that there are two inflection points of inhibition of PMN chemotaxis, one at 10% serum and a second one at about 50%. This is a highly reproducible curve, even though the second point of inflection does not appear to be great.

So my first question would be whether or not there are other inhibitors in Dr. Mannick's serum which might correspond to these findings.

(slide) Utilizing the concept that there were two inhibitors, we looked at G-200 Sephadex chromatography and found that there are again two inhibitors of chemotaxis. Data are confirmed using sucrose density gradients, as well as isoelectric focusing. These inhibitors are about 360,000 and 120,000 molecular weight.

More recently, we found smaller inhibitors, and it leads to my basic question. I wonder if Dr. Mannick could comment upon the nature of these multiple inhibitors, and whether they are all part of a common, or similar, immunoregulatory system.

DR. DONALD L. MORTON (Los Angeles, California): Dr. Jack Roth and I have done some studies with conclusions somewhat similar to those of Dr. McLoughlin and his colleagues.

We looked at the effect of surgical trauma on immunosuppression in patients with cancer, but our data were organized in a slightly different way. We compared patients with minor trauma, such as that from regional lymphadenectomy, with patients whose operative procedures invaded the thoracic or abdominal cavities. We found no correlation with the length of operation but did find that, if the abdominal or thoracic cavities were entered, the patients were more immunosuppressed. Also, if tumor was completely resected, immunosuppressive factors disappeared even in patients who were anergic preoperatively and who had major surgical trauma.

In our series there was a correlation between blood transfusion and degree and duration of immunosuppression. The most immunosuppressed patients were those undergoing cardiopulmonary bypass.

The duration of immunosuppression in our series was similar. One patient was immunosuppressed for six weeks, but usually the patient's immunocompetence returned in seven to ten days.

Finally, I would like to ask Dr. Mannick if there was a difference in the degree of immunosuppression between patients who had cardiopulmonary bypass and those who had major aortic resections.

DR. STANLEY M. LEVENSON (Bronx, New York): I wonder if Dr. Mannick can tell us something about the specific amino acid composition of the active fraction or fractions. I am interested in that particularly because in the late '40's and early '50's my colleagues and I described an amino conjugate fraction which appeared in the serum of previously healthy animals and previously healthy men who were injured. The concentration of this fraction correlated with the severity of the injury. It is a dialyzable compound, or group of compounds, and increased remarkably in patients with renal dysfunction.

I was wondering whether there may be some similarity between the active fraction or fractions Dr. Mannick and his colleagues have isolated and the amino conjugate fraction we worked with in terms of amino acid composition. I would also like to ask Dr. Mannick if he has looked at patients with renal dysfunction following injury, to see whether there is a still higher increase in the fraction or fractions he is looking at. If so, this may be one of the reasons why a patient with renal failure is particularly susceptible to infection.

DR. JOHN A. MANNICK (Closing discussion): In reply to Dr. Clowes, I do believe that we are now finding some functions for that myriad of polypeptide molecules that circulate around in everyone's serum, whose function has heretofore been unknown, and I suppose that they represent a few words in the biochemical language that cells use to communicate with one another, and that language has by no means been translated yet.

I don't know what relationship the factors that Dr. Clowes has been working with have to the one we have been talking about. I am not sure whether our factor has any metabolic effect on lymphocytes that is other than transient, simply because cells that do not rosette very well from traumatized patients in our laboratory upon washing multiple times will then rosette quite actively, and the wash material does contain the sort of molecule we have been talking about.

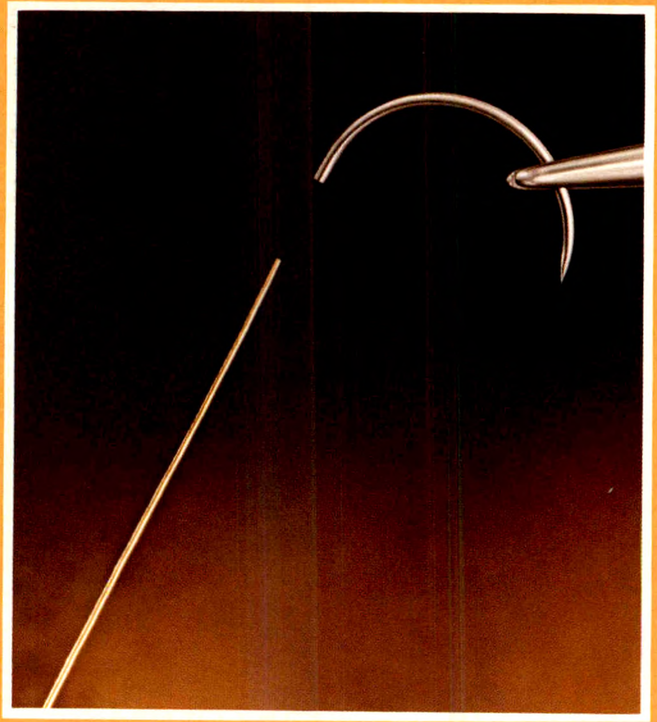
In answer to Dr. Meakins, I think that his idea is an intriguing one; namely, that the immunoregulatory system may have some features similar to the complement system; for example, breakdown products of one activity may subsume other activities, and we may be talking about pieces of molecules that once did something else, and now affect a different cell type. I think that is perfectly possible, but I don't know anything else to say about it at this time, other than to admit the possibility.

In reply to Dr. Morton, cardiopulmonary bypass patients and aneurysm resection patients, which were the two groups we were looking at, really behaved the same in terms of percentage that developed anergy and the percentage that had suppressive serum. So in this instance, surprisingly enough, cardiopulmonary bypass did not seem to be any different than aneurysm resection.

In answer to Dr. Levenson, I have been intrigued by that early paper of his, and he may be right. He may, in fact, have identified this material. I just don't know whether they are similar or not. The amino acid composition of our material I don't think I can give him with any confidence. We do have a sample of this material in the hands of the Molecular Biology Institute at Hoffman-La Roche, and we hope to have some information about its true nature in a few weeks.

NOW.
The needle/suture combination you've been waiting for...

SURGICAL GUT ON CONTROL RELEASE* NEEDLES



only from
ETHICON
the closing word

©ETHICON, INC. 1978 *Trademark

A major alternative to codeine combinations in moderate to moderately severe pain

vicodin® CIII

hydrocodone bitartrate 5 mg. with acetaminophen 500 mg.

A unique narcotic analgesic formula with hydrocodone– a semi-synthetic analogue of codeine

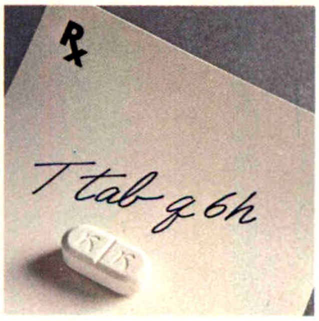
combined with 500 mg. acetaminophen

Individual patient rating of treatment acceptability of VICODIN,® Tylenol® with Codeine No. 3, and placebo by 90 post-partum patients.

In a controlled double-blind study, 3 groups of 30 women with moderate episiotomy pain were treated with VICODIN,® Tylenol® with Codeine No. 3 or placebo[1]

	VICODIN®	Tylenol® with Codeine No. 3	Placebo
VERY GOOD	73% 22 of 30 patients	50% 15 of 30 patients	33% 10 of 30 patients
FAIR/ POOR	27% 8 of 30 patients	50% 15 of 30 patients	67% 20 of 30 patients

DOSAGE CAN BE TITRATED TO MATCH THE SEVERITY OF PAIN



The usual adult dose is one tablet every 6 hours as needed for pain. In cases of more severe pain, two tablets every 6 hours or one tablet more frequently than every 6 hours may be required. VICODIN® is given orally. VICODIN Tablets are scored and can be easily divided for greater dosage flexibility.

Convenient telephone prescribing and ℞ refills.

Telephone prescribing is permissible in most states. Up to 5 refills in 6 months where state law permits.

---

[1] Hopkinson, J. III: Vicodin. A new analgesic: Clinical evaluation of efficacy and safety of repeated doses. Curr. Ther. Res. 24(6):633-645, 1978.

Please see next page for prescribing information

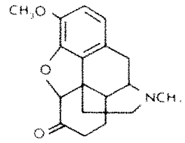
vicodin® ©III

hydrocodone bitartrate 5 mg. with acetaminophen 500 mg.

Description: Each tablet of VICODIN contains:
Hydrocodone Bitartrate 5 mg.
Warning: May be habit forming.
Acetaminophen (APAP) 500 mg.

Acetaminophen occurs as a white, odorless crystalline powder, possessing a slightly bitter taste.

The hydrocodone component is dihydrocodeinone, a white, odorless crystalline powder which is derived from the opium alkaloid, thebaine, and may be represented by the following structural formula.



Actions: The principal analgesic ingredient, hydrocodone, is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine; most of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the hydrocodone in this drug are analgesia and sedation.

Hydrocodone is similar to codeine and methadone in that it retains at least one half of its analgesic activity when administered orally.

This drug also contains the non-narcotic antipyretic-analgesic acetaminophen.

Indications: For the relief of moderate to moderately severe pain.

Contraindications: Hypersensitivity to hydrocodone or acetaminophen.

Warnings: Drug Dependence: Hydrocodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, VICODIN (hydrocodone bitartrate with acetaminophen) is subject to the Federal Controlled Substances Act.

Usage in Ambulatory Patients: Hydrocodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Interaction with other central nervous system depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with hydrocodone and acetaminophen may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, VICODIN should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children: VICODIN should not be administered to children.

Precautions: Head injury and increased intracranial pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of VICODIN or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients: VICODIN should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease and prostatic hypertrophy or urethral stricture.

Adverse Reactions: The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

Dosage and Administration: The usual adult dose is one tablet every 6 hours as needed for pain. In cases of more severe pain, two tablets every 6 hours or one tablet more frequently than every 6 hours may be required. VICODIN is given orally.

Drug Interactions: The CNS depressant effects of this drug may be additive with that of other CNS depressants. See **Warnings.**

Management of Overdosage: Signs and Symptoms: Serious overdose with VICODIN (hydrocodone bitartrate with acetaminophen) is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of this drug may, in addition, result in acute hepatic toxicity.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including hydrocodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressor and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug. Acetaminophen in massive overdosage may cause hepatotoxicity in some patients. Clinical and laboratory evidence of hepatotoxicity may be delayed for up to one week. Close clinical monitoring and serial hepatic enzyme determinations are therefore recommended.

Treatment of acute acetaminophen overdosage is purely symptomatic.

How Supplied: Bottles of 100 white, bisected, flat capsule-shaped tablets with a double K logo.

Knoll Pharmaceutical Company, Whippany, New Jersey 07981
Member Company, Certified Medical Representatives Institute, Inc. 5629

ATLAS OF APPLIED VASCULAR SURGERY

■

By KIYOSHI INOKUCHI, M.D.,

and AKIRA KUSABA, M.D.

Here is a unique and timely atlas text describing the wide variety of diseases and lesions that have been successfully treated through vascular anastomoses performed with a new stapling instrument originated and perfected by Dr. Inokuchi.

The extensive experiences of the authors with vessel suturing equipment have extended the use of these instruments beyond the repair and reconstruction of vessels, to other areas of surgery. For example, use of the Inokuchi stapling instrument has made possible the free transplantation of intestine as a reconstruction of the cervical esophagus.

A highlight of the book is a discussion of the many problems and difficulties which arise in portacaval shunt for portal hypertension. The authors have realized success in this operation and describe a new technique—left gastric venous-caval shunt.

This highly descriptive book contains details on the design of the Inokuchi vascular stapler and step-by-step instructions on its use and applications. Many of the operations performed utilizing the device are discussed, describing the techniques used and giving case histories.

198 pages / 301 illustrations, including 68 photographs.
11 in color / 21 Tables / 1975 / $57.00

Lippincott

J. B. Lippincott Company
East Washington Square • Phila., Pa. 19105

Please send me:

☐ ATLAS OF APPLIED VASCULAR SURGERY $57.00

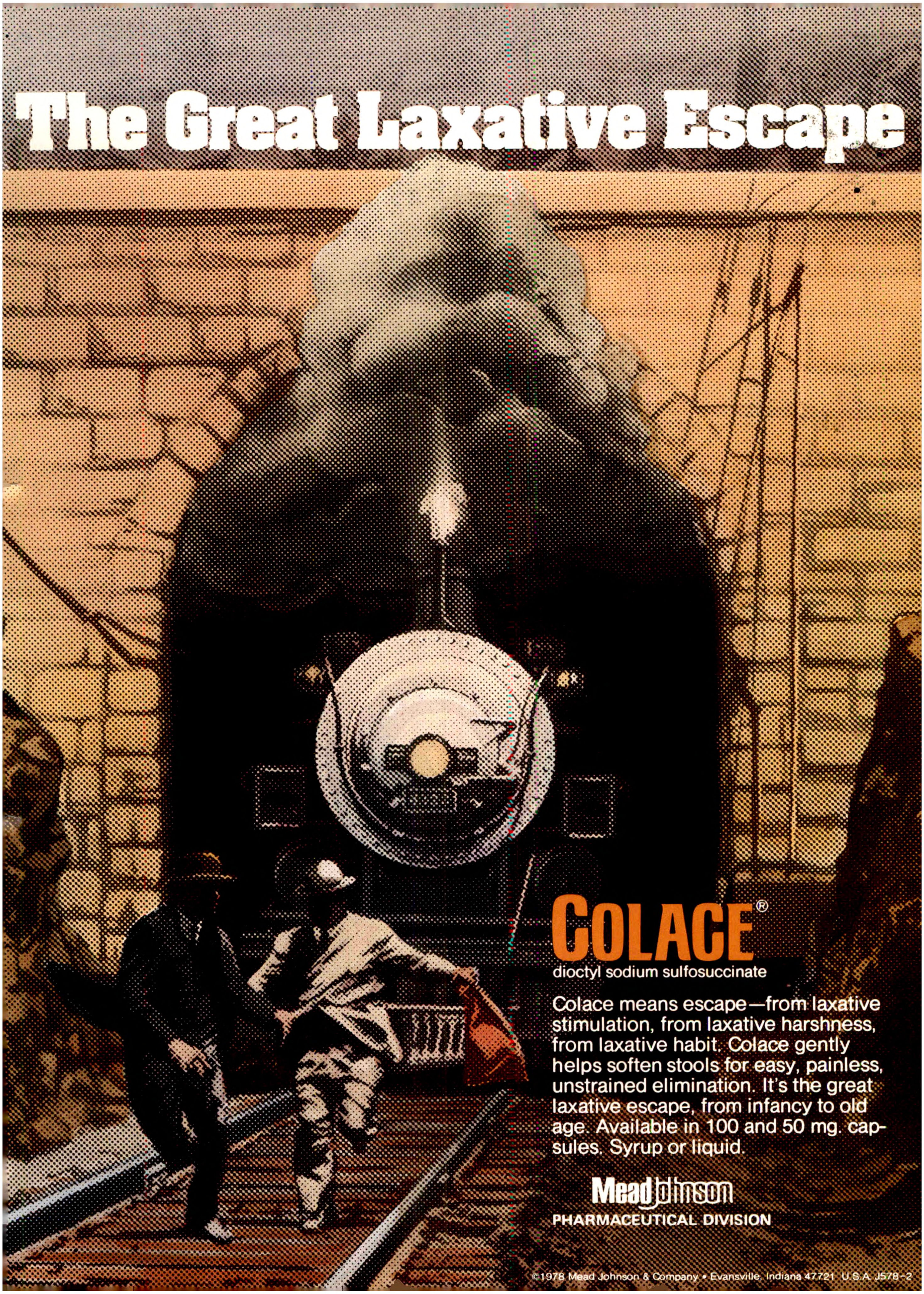
Name ____________________

Address ____________________

City ______________ State ________ Zip ________

☐ Payment enclosed Save postage & handling ☐ Charge and bill me Plus postage & handling

Also available at your medical bookstore AS 9/79



COLACE®

dioctyl sodium sulfosuccinate

Colace means escape—from laxative stimulation, from laxative harshness, from laxative habit. Colace gently helps soften stools for easy, painless, unstrained elimination. It's the great laxative escape, from infancy to old age. Available in 100 and 50 mg. capsules. Syrup or liquid.

MeadJohnson

PHARMACEUTICAL DIVISION

©1978 Mead Johnson & Company • Evansville, Indiana 47721 U.S.A. J578-2

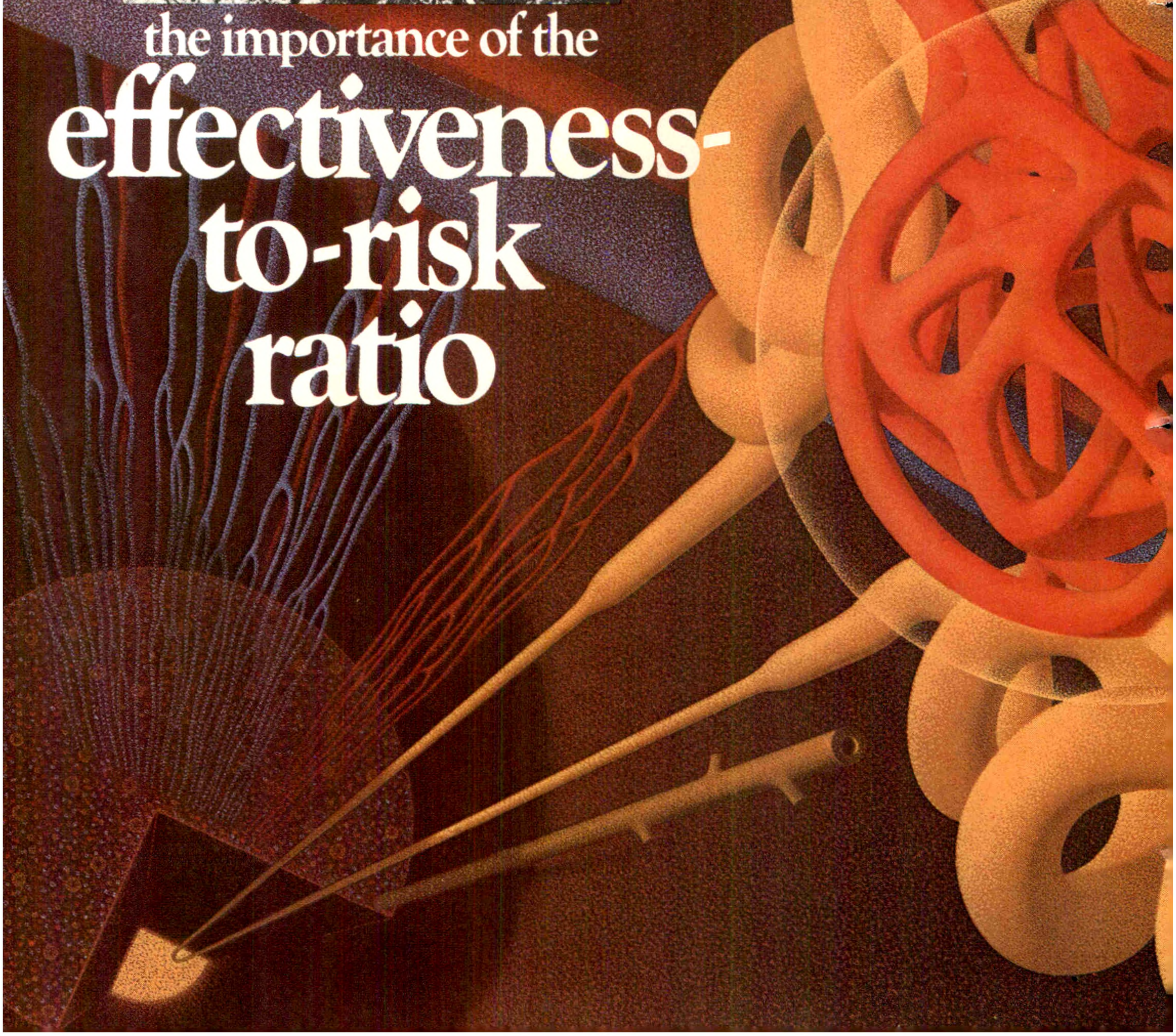
Selecting an aminoglycoside:

Brush-border membrane of proximal tubule (11,400×).

the importance of the effectiveness-to-risk ratio

In patients with serious bacterial infection, the choice of antibiotic therapy is usually made on the basis of the effectiveness-to-risk ratio. This consideration is particularly important when an aminoglycoside antibiotic is indicated.

The activity of Nebcin® (tobramycin sulfate, Lilly) against a wide range of gram-negative organisms is now well known. A review of worldwide literature shows "that tobramycin has significant antibacterial activity and that it is the most potent of all aminoglycosides against *P. aeruginosa.* The antibacterial



activities of tobramycin and gentamicin against members of the Enterobacteriaceae are comparable, with each agent possessing slightly greater activity than the other against selected strains of any species."[1]

Nebcin is indicated in the treatment of

- septicemia
- serious lower respiratory infections
- gastrointestinal infections, including peritonitis
- serious complicated and recurrent urinary tract infections
- serious skin, bone, and soft-tissue infections, including burns

caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa, Escherichia coli, Proteus* sp. (indole-positive and indole-negative), *Providencia, Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

The proximal tubule

The proximal tubule is the site in the renal system where aminoglycosides produce nephrotoxicity.

An investigator has studied the urinary excretion of alanine aminopeptidase, a principal enzyme of the brush-border membrane of the proximal tubule.[2] Levels of the enzyme become elevated in the urine as a result of toxic lesions in acute tubular necrosis or of inflammatory processes in the kidney, such as rejection crisis. In measurements of the effect of aminoglycosides (administered for three consecutive days) on the excretion of this enzyme by healthy humans, tobramycin appeared to have a minimum effect on the brush-border membrane.

Another investigative team has studied the relationship between tissue concentration and toxicity.[3] The toxicity of aminoglycosides may be related to the degree of their binding to tissue. Hence, aminoglycosides that accumulate less may be less nephrotoxic.

All aminoglycosides are potentially nephrotoxic and ototoxic. Therefore, patients should be monitored closely when aminoglycosides are being used. Patients with impaired renal function, the elderly, those with underlying disease, those with prior exposure to potentially nephrotoxic agents, and those with poor host resistance are at special risk. During clinical trials in 3506 patients treated with tobramycin, investigators reported drug-related nephrotoxicity in 1.5 percent (53 patients).[4]

In view of the effectiveness of Nebcin and the relatively low risk of nephrotoxicity, tobramycin can be an appropriate choice for patients requiring aminoglycoside therapy.

References

1. J. Infect. Dis., *134* (Supplement):S3, 1976.
2. J. Antimicrob. Chemother., *4* (Supplement A):23, 1978.
3. J. Antimicrob. Chemother., *4* (Supplement A):53, 1978.
4. Med. J. Aust., *2* (Special Supplement):22, 1977.

◆ I.M./I.V.

tobramycin/Nebcin®

tobramycin sulfate

80 mg* in 2-ml ampoules

*Equivalent to tobramycin.

Please see following page for a brief summary of the prescribing information.

800730

♦ I.M./I.V.
Nebcin®
tobramycin sulfate

Summary of Prescribing Information

> **WARNINGS**
>
> Patients treated with Nebcin should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.
>
> Both vestibular and auditory ototoxicity can occur. Eighth-nerve impairment may develop if patients have preexisting renal damage and if Nebcin is administered for longer periods or in higher doses than those recommended.
>
> Tobramycin is potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by cylindruria, oliguria, proteinuria, or evidence of nitrogen retention (increasing BUN, NPN, or creatinine). Evidence of impairment in renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.
>
> Nebcin should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.
>
> In the case of overdosage or toxic reactions, peritoneal dialysis or hemodialysis will help remove tobramycin from the blood.
>
> Serum concentrations should be monitored when feasible, and prolonged concentrations above 12 mcg/ml should be avoided. Urine should be examined for increased excretion of protein, cells, and casts.
>
> Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, and vancomycin, should be avoided.
>
> Nebcin should not be given concurrently with potent diuretics. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.
>
> *Usage in Pregnancy*—Safety of this product for use during pregnancy has not been established.

Description: Tobramycin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from the actinomycete *Streptomyces tenebrarius.* Nebcin Injection is a clear and colorless sterile aqueous solution for parenteral administration. It is stable and requires no refrigeration.

Indications and Usage: Nebcin is indicated for the treatment of serious infections caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa, Escherichia coli, Proteus* sp. (indole-positive and indole-negative), *Providencia, Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

Nebcin is indicated in the treatment of septicemia; central-nervous-system infections, including meningitis; neonatal sepsis; serious lower respiratory infections; gastrointestinal infections, including peritonitis; and serious skin, bone, and soft-tissue infections, including burns, caused by the susceptible organisms listed above. Clinical studies have shown Nebcin also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Nebcin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that the causative organisms are resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom gram-negative septicemia, neonatal sepsis, or meningitis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Nebcin may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the WARNINGS box above.

Contraindication: A history of hypersensitivity to tobramycin is a contraindication to its use.

Warnings: *See* WARNINGS box above.

Precautions: Specimens should be collected during therapy for examination, as recommended in the WARNINGS box.

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg/kg). The possibility that prolonged or secondary apnea may occur should be considered if tobramycin is administered to anesthetized patients who are also receiving neuromuscular blocking agents, such as succinylcholine or tubocurarine.

Cross-allergenicity among aminoglycosides has been demonstrated.

If overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

Adverse Reactions: *Nephrotoxicity*—Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, cylindruria, and increased proteinuria, have been reported, especially in patients with a history of renal impairment who are treated for longer periods or with higher doses than those recommended.

Neurotoxicity—Adverse effects on both the vestibular and auditory branches of the eighth nerve have been noted, especially in patients receiving high doses or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss.

NOTE: The risk of toxic reactions is low in patients with normal renal function who do not receive Nebcin in higher doses or for longer periods of time than those recommended.

Other reported adverse reactions possibly related to Nebcin include increased serum transaminase (SGOT, SGPT) and increased serum bilirubin; anemia, granulocytopenia, and thrombocytopenia; and fever, rash, itching, urticaria, nausea, vomiting, headache, and lethargy.

Suggested Dosage Guides—I.M./I.V.:

The usual duration of treatment is seven to ten days.

Usual dosage for adults, children, and older infants (normal renal function)—

3 mg/kg/day administered in three equal doses every eight hours. In life-threatening situations, the dosage may be increased up to 5 mg/kg/day administered in three or four equal doses. This dosage should be reduced to 3 mg/kg/day as soon as clinically indicated. (Refer to Table 1 for dosage schedule.)

Dosage for neonates up to one week of age (normal renal function)—

Up to 4 mg/kg/day may be given in two equal doses every 12 hours.

Dosage guidelines for adult or pediatric patients with reduced renal function—

After a loading dose of 1 mg/kg, subsequent dosage must be adjusted either with reduced doses at eight-hour intervals or with normal doses at prolonged intervals. To determine the reduced dose at eight-hour intervals, see the convenient nomogram in the package literature.[*] To calculate normal dosage at prolonged intervals (if the creatinine clearance rate is not available and the patient's condition is stable), the following formula may be used:

$$1 \text{ mg/kg q } (6 \times \text{ serum creatinine}) \text{ h}$$

Neither regimen should be used when dialysis is being performed.

I.V. Administration—The usual volume of diluent for adults is 50 to 100 ml. For children, the volume of diluent should be proportionately less than for adults. The diluted solution usually should be infused over a period of 20 to 60 minutes.

---

[*] An alternate rough guide for determining reduced dosage at eight-hour intervals (for patients whose steady-state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine.

Table 1. Dosage Schedule Guide for Adults with Normal Renal Function
(Dosage at Eight-Hour Intervals)

For Patient Weighing kg	lb	Usual Dose for Serious Infections 1 mg/kg q 8 h (Total, 3 mg/kg/day)		Maximum Dose for Life-Threatening Infections **(Reduce as soon as possible)** 1.66 mg/kg q 8 h (Total, 5 mg/kg/day)	
		mg/dose	**ml/dose[†]**	**mg/dose**	**ml/dose[†]**
		q 8 h		**q 8 h**	
120	264	120 mg	3 ml	200 mg	5 ml
115	253	115 mg	2.9 ml	191 mg	4.75 ml
110	242	110 mg	2.75 ml	183 mg	4.5 ml
105	231	105 mg	2.6 ml	175 mg	4.4 ml
100	220	100 mg	2.5 ml	166 mg	4.2 ml
95	209	95 mg	2.4 ml	158 mg	4 ml
90	198	90 mg	2.25 ml	150 mg	3.75 ml
85	187	85 mg	2.1 ml	141 mg	3.5 ml
80	176	80 mg	2 ml	133 mg	3.3 ml
75	165	75 mg	1.9 ml	125 mg	3.1 ml
70	154	70 mg	1.75 ml	116 mg	2.9 ml
65	143	65 mg	1.6 ml	108 mg	2.7 ml
60	132	60 mg	1.5 ml	100 mg	2.5 ml
55	121	55 mg	1.4 ml	91 mg	2.25 ml
50	110	50 mg	1.25 ml	83 mg	2.1 ml
45	99	45 mg	1.1 ml	75 mg	1.9 ml
40	88	40 mg	1 ml	66 mg	1.6 ml

[†] Applicable to all product forms except Nebcin, Pediatric, Injection (see How Supplied).

How Supplied: Ampoules (Vials) Nebcin® (tobramycin sulfate, Lilly), Injection, 80 mg (equivalent to tobramycin) per 2 ml, 2 ml, rubber-stoppered, in packages of 1 and Traypaks™ (multivial cartons, Lilly) of 25.

Ampoules (Vials) Nebcin, Pediatric, Injection, 20 mg (equivalent to tobramycin) per 2 ml, 2 ml, rubber-stoppered, in packages of 1.

Hyporets® (disposable syringes, Lilly) Nebcin, Injection, 60 mg (equivalent to tobramycin) per 1.5 ml, 1.5 ml, and 80 mg (equivalent to tobramycin) per 2 ml, 2 ml, in packages of 24.

Each ml also contains 5 mg phenol as a preservative, 3.2 mg sodium bisulfite, 0.1 mg edetate disodium, and water for injection, q.s. Sulfuric acid and/or sodium hydroxide may have been added to adjust the *p*H. [030476C]

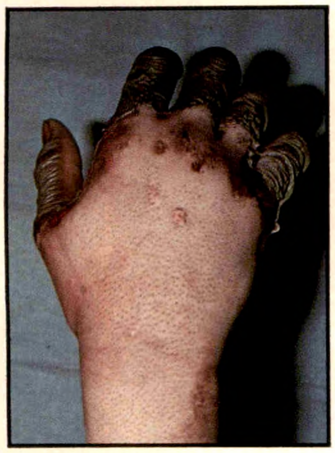
Additional information available to the profession
on request from Eli Lilly and Company,
Indianapolis, Indiana 46206.

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

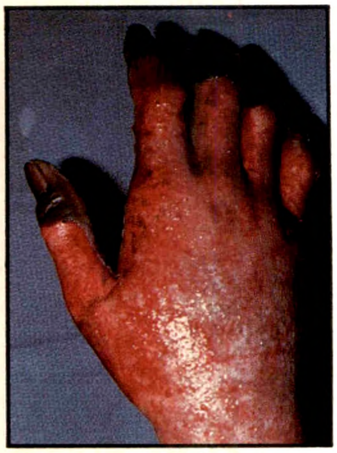
800646

NEW TECHNIQUE IN THE TREATMENT OF DEEP DERMAL HAND BURN

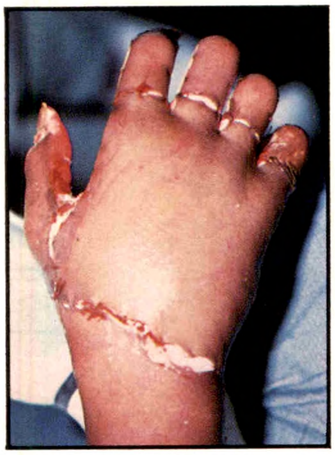
ENZYMATIC DEBRIDEMENT WITH IMMEDIATE GRAFT[1]



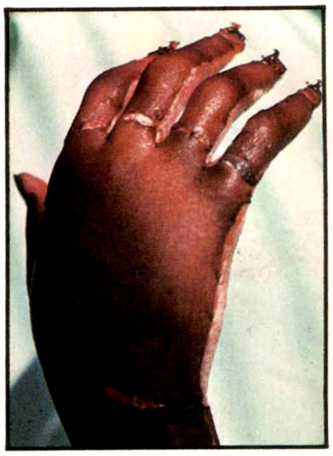
2 hours postburn on admission



24 hours postburn



Graft applied 24 hours postburn



5 days postburn

Technique:

1. Apply TRAVASE® Ointment (Sutilains Ointment, NF) upon admission (within 24 hours of burn injury).
2. Repeat every 12 hours until debridement produces punctate dermal bleeding.
3. After 24 hours, if debridement is incomplete, add an appropriate antimicrobial.
4. Graft as soon as punctate dermal bleeding is produced (within 24 to 36 hours postburn).
5. Remove dressings four days postgraft and initiate return to motion.

The use of this new technique, utilizing TRAVASE® Ointment, is an interesting development in the treatment of deep dermal hand burns. The speed of debridement and rapidity of healing obtained with TRAVASE Ointment makes this new technique possible.

Advantages:

- Preserves viable tissue
- Achieves early skin cover
- Initiates early range of motion
- Reduces likelihood of blood loss and surgery
- Shortens hospitalization and period of disability
- Minimizes hypertrophic scarring

TRAVASE® OINTMENT
(Sutilains Ointment, NF)

TRAVASE® Ointment
(Sutilains Ointment NF)

Indications: For wound debridement. TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:

Second and third degree burns.
Decubitus ulcers.
Incisional, traumatic, and pyogenic wounds.
Ulcers secondary to peripheral vascular disease.

Contraindications: Application of TRAVASE Ointment is contraindicated in the following conditions:

Wounds communicating with major body cavities.
Wounds containing exposed major nerves or nervous tissue.
Fungating neoplastic ulcers.
Wounds in women of child-bearing potential—because of lack of laboratory evidence of effects of TRAVASE Ointment upon the developing fetus.

Warning: Do not permit TRAVASE Ointment to come into contact with the eyes. If contact is made, immediately rinse with copious amounts of water, preferably sterile.

Precautions: A moist environment is essential to optimal activity of the enzyme. Enzyme activity may also be impaired by certain agents (see package insert). Although there have been no reports of systemic allergic reaction in humans, studies have shown that there may be an antibody response in humans to absorbed enzyme material.

Adverse Reactions: Consist of mild, transient pain, paresthesias, bleeding and transient dermatitis. Pain usually can be controlled by administration of mild analgesics. Side effects severe enough to warrant discontinuation of therapy occasionally have occurred.

If bleeding or dermatitis occurs as a result of the application of TRAVASE Ointment, therapy should be discontinued. No systemic toxicity has been observed as a result of the topical application of TRAVASE Ointment.

DOSAGE AND ADMINISTRATION: STRICT ADHERENCE TO THE FOLLOWING IS REQUIRED FOR EFFECTIVE RESULTS OF TREATMENT.

1. Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials which may denature enzyme or alter substrate characteristics (e.g., hexachlorophene, silver nitrate, benzalkonium chloride, nitrofurazone).
2. Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g., sodium chloride or water solutions).
3. Apply TRAVASE Ointment in a thin layer assuring intimate contact with necrotic tissue and complete wound coverage extending ¼ to ½ inch beyond the area to be debrided.
4. Apply loose wet dressings.
5. Repeat entire procedure 3 to 4 times per day for best results.

How Supplied: TRAVASE Ointment (Sutilains Ointment, NF) is supplied sterile in one-half ounce (14.2 gm) tubes. Each gram contains 82,000 casein units of proteolytic activity in a hydrophobic ointment base.

The ointment must be stored under refrigeration at 2° to 8° C (35° to 46° F).

U.S. Patent No. 3,409,719

8-19-20-137A August 1976

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

© Copyright 1979 Travenol Laboratories, Inc.

---

1. Lassa R: Presentation at American Plastic & Reconstructive Surgery Meeting and Hand Society Meeting, Hollywood, FL, November, 1978.

Fifth Edition

Rhoads
TEXTBOOK OF SURGERY
Principles and Practice

●

Edited by JAMES D. HARDY, M.D.
with 279 contributors

Although technically a Fifth Edition of *Surgery: Principles and Practice*, this revision is new in *title, editor, contributing authors, content, approach, and format.* It has been reorganized into three major parts: General Principles of Surgical Practice; Specific Lesions and Dysfunctions Involving Various Organs; and Parasurgical Considerations.

The approach is now problem-oriented and this outstanding volume considers virtually all current problems in surgery.

More than 270 contributors give you an enormous geographical and philosophical range in one volume. Each is well known in his field and discusses management of a specific problem. Included in each of the hundreds of topics discussed are basic features of the operation including a table of basic facts; an overview of the concept under discussion; description of specific pathological conditions; surgical history; physiology; a pathophysiological diagram and an anatomical sketch whenever feasible; many excellent illustrations of disease processes and treatment procedures; possible technical errors; safeguards; postoperative problems; and complications.

2354 Pages / 1738 Illustrations / 313 Tables
5th Edition, 1977 / One Volume Format: $38.50
Two Volume Format: $45.00

Now Available in Either One or Two Volume Form!

Lippincott

J. B. LIPPINCOTT COMPANY
East Washington Square ● Phila., Pa. 19105

In Canada: J. B. Lippincott Company of Canada Ltd.
75 Horner Avenue, Toronto, Ontario M8Z 4X7

Please send me:
Rhoads TEXTBOOK OF SURGERY
☐ 1 Vol. $38.50 ☐ 2 Vols. $45.00

Name ______________________________

Address ______________________________

City ______________ State _______ Zip _________

☐ Payment enclosed (Save postage and handling)
☐ Charge and bill me (Plus postage and handling)

Also available at your medical bookstore. AS 9/79

Tablets
PERCODAN®
oxycodone with APC Ⓒ II

Tablets
PERCODAN®-Demi
oxycodone with APC Ⓒ II

Brief Summary of Prescribing Information

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN® and PERCODAN®-Demi, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® and PERCODAN®-Demi are subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® and PERCODAN®-Demi should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® and PERCODAN®-Demi may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® and PERCODAN®-Demi should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children. PERCODAN®-Demi, containing half the amount of oxycodone, can be considered.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN® and PERCODAN®-Demi or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® and PERCODAN®-Demi should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCODAN® and PERCODAN®-Demi are given orally.

PERCODAN® The usual adult dose is one tablet every 6 hours as needed for pain.

PERCODAN®-Demi Adults—One or two tablets every six hours. Children 12 years and older—One-half tablet every six hours. Children 6 to 12 years—One-quarter tablet every six hours. PERCODAN®-Demi is not indicated for children under 6 years of age.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® and PERCODAN®-Demi may be additive with that of other CNS depressants. See WARNINGS.

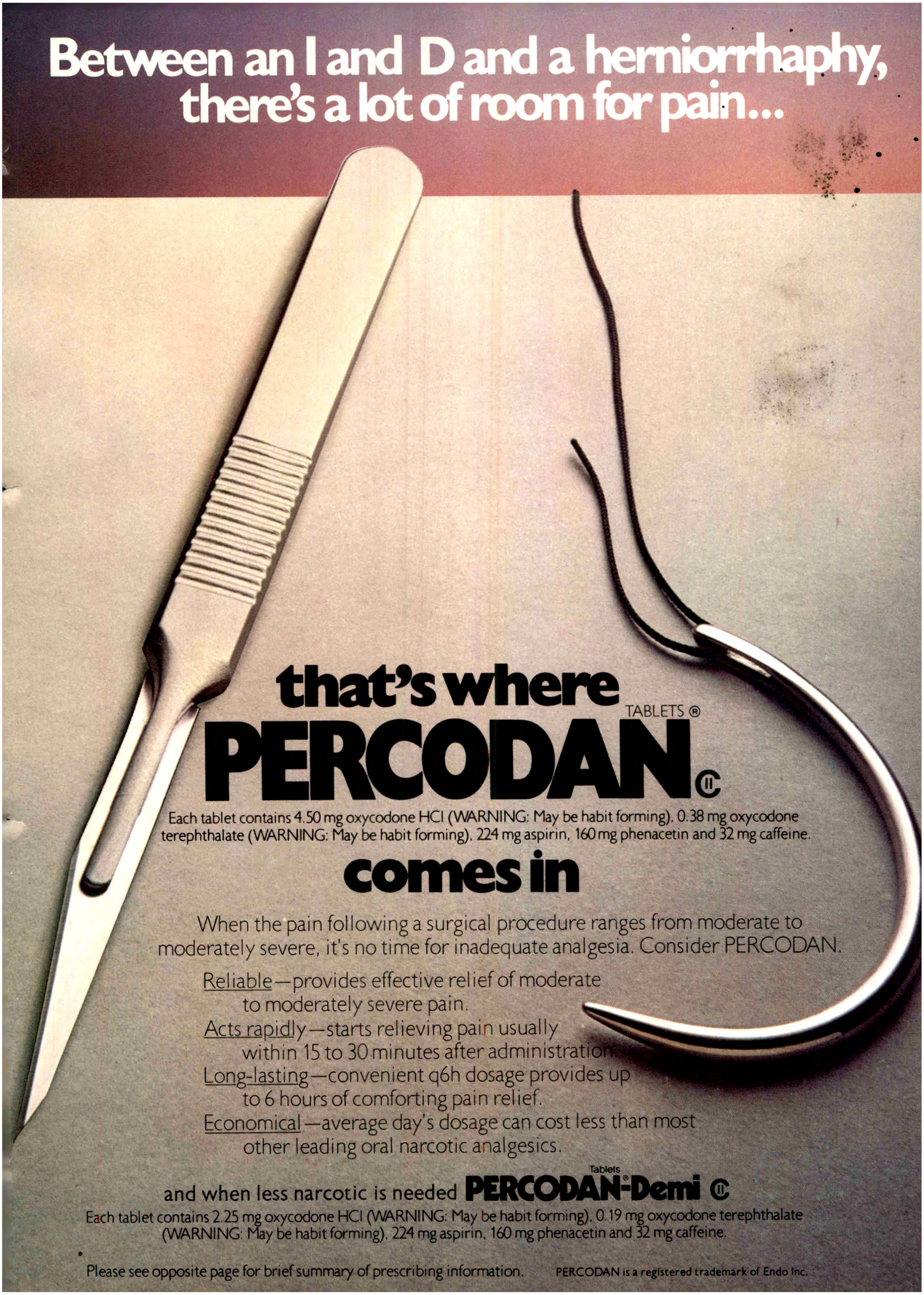
Aspirin may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

DEA Order Form Required. 6074-1/6078-1BS

Endo Inc.
Manati, Puerto Rico
DUPONT

Subsidiary of Endo Laboratories Inc.
Subsidiary of the DuPont Company

EDO-437P479



Between an I and D and a herniorrhaphy, there's a lot of room for pain...

that's where PERCODAN TABLETS ® Ⓒ II

Each tablet contains 4.50 mg oxycodone HCl (WARNING: May be habit forming), 0.38 mg oxycodone terephthalate (WARNING: May be habit forming), 224 mg aspirin, 160 mg phenacetin and 32 mg caffeine.

comes in

When the pain following a surgical procedure ranges from moderate to moderately severe, it's no time for inadequate analgesia. Consider PERCODAN.

Reliable—provides effective relief of moderate to moderately severe pain.

Acts rapidly—starts relieving pain usually within 15 to 30 minutes after administration.

Long-lasting—convenient q6h dosage provides up to 6 hours of comforting pain relief.

Economical—average day's dosage can cost less than most other leading oral narcotic analgesics.

and when less narcotic is needed **PERCODAN®-Demi Tablets** Ⓒ II

Each tablet contains 2.25 mg oxycodone HCl (WARNING: May be habit forming), 0.19 mg oxycodone terephthalate (WARNING: May be habit forming), 224 mg aspirin, 160 mg phenacetin and 32 mg caffeine.

Please see opposite page for brief summary of prescribing information.

PERCODAN is a registered trademark of Endo Inc.

See below for important product information concerning warnings, adverse reactions, patient selection and prescribing and precautionary recommendations.

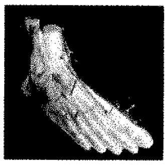
More pain-free time for procedures

Marcaine® hydrochloride

brand of

bupivacaine hydrochloride

with or without epinephrine 1:200,000



Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

Allergic reactions, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

References:

1. Moore DC, Bridenbaugh LD, Thompson GE, et al: Bupivacaine: a review of 11,080 cases. *Anesth Analg* 57:42-53, 1978.

BREON BREON LABORATORIES, INC.
90 Park Avenue, New York, N.Y. 10016

FORMULA

PRODUCT IDENTIFICATION			MULTIPLE DOSE VIAL						SINGLE DOSE AMPUL				
Marcaine HCl (brand of bupivacaine HCl) %	mg./ml.	Epinephrine* (as bitartrate) Dilution	Methylparaben mg./ml.	Sodium Bisulfite mg./ml.	Thioglycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.	Sodium Bisulfite mg./ml.	Thioglycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.
0.25	2.5	—	1	—	—	—	—	—	—	—	—	—	—
0.25	2.5	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.5	5.0	—	1	—	—	—	—	—	—	—	—	—	—
0.5	5.0	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.75	7.5	—							—	—	—	—	—
0.75	7.5	1:200,000	Not Available in Vials						.5	.001	2	.0017	0.1

Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved.

Federal law prohibits dispensing without a prescription.

More pain-free time for procedures

A duration of action that is two to three times longer than lidocaine or mepivacaine.[1]

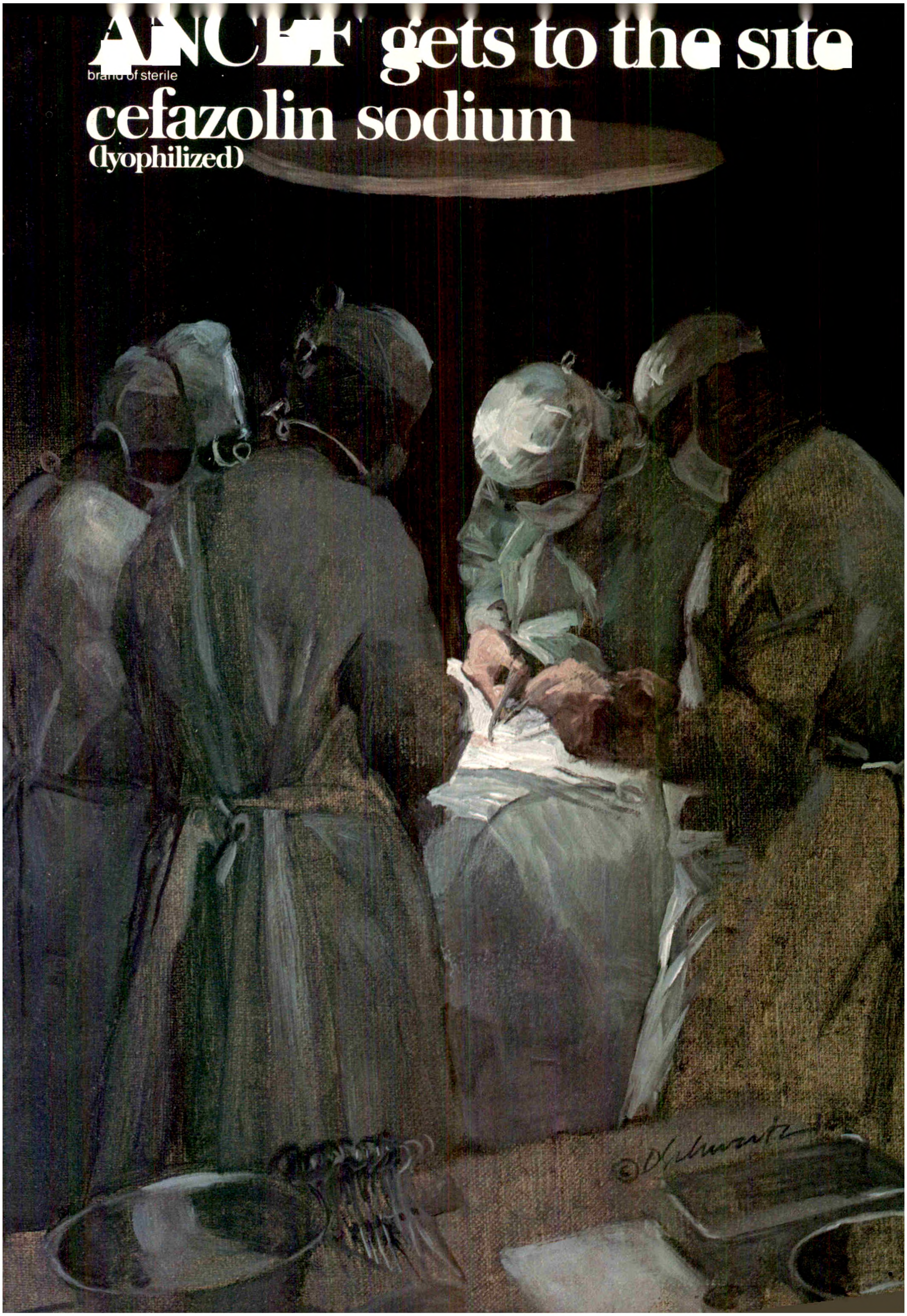
Marcaine® hydrochloride

brand of

bupivacaine hydrochloride

with or without epinephrine 1:200,000

See adjacent page for prescribing information. Resuscitative equipment and drugs should be readily available when any local anesthetic is used.
Model from the scientific exhibit, Nerve Blocks of the Foot, by Raymond Locke, D.P.M. and Steven E. Locke, M.D.


ANCEF gets to the site
brand of sterile
cefazolin sodium
(lyophilized)

to help eliminate infections*

Most infections can be treated with 500 mg. or 1 gram of 'Ancef' every 8 hours.

***'Ancef' is indicated in the treatment of the following serious infections due to susceptible organisms:**

Respiratory tract infections due to *Streptococcus pneumoniae* (formerly *D. pneumoniae), Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Urinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin structure infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), group A beta-hemolytic streptococci and other strains of streptococci.

Biliary tract infections due to *Escherichia coli,* various strains of streptococci, *Proteus mirabilis, Klebsiella* species, and *Staphylococcus aureus.*

Bone and joint infections due to *Staphylococcus aureus.*

Genital infections (i.e., prostatitis, epididymitis) due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterococci.

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae), Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

ANCEF® IV IM

brand of sterile

CEFAZOLIN SODIUM

(LYOPHILIZED)

Injection: 250 mg., 500 mg., and 1 gram vials

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Contraindications: ANCEF (STERILE CEFAZOLIN SODIUM, SK&F) IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

Warnings: BEFORE CEFAZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to 'Ancef'.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

Precautions: Prolonged use of 'Ancef' may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

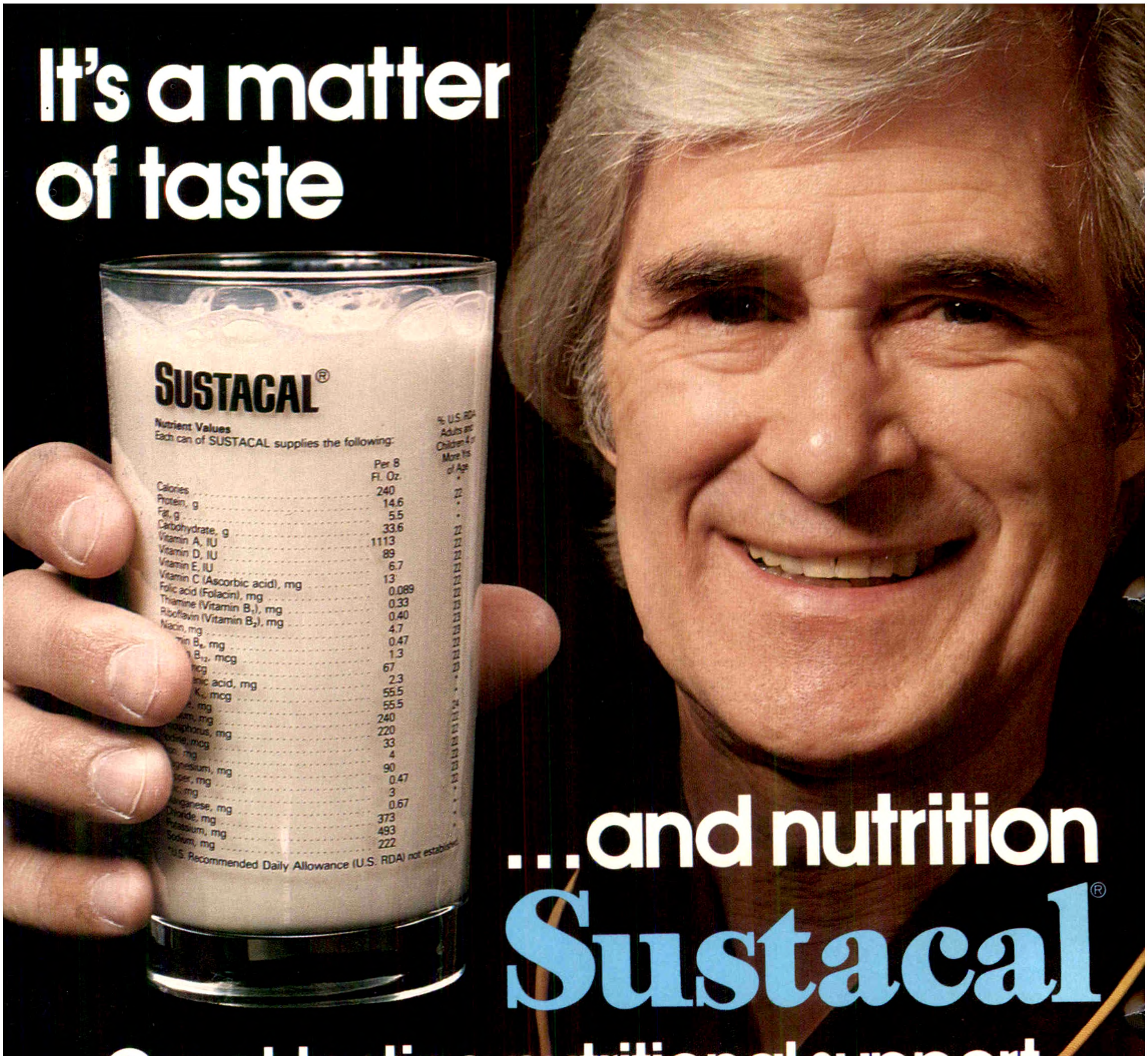
Adverse Reactions: The following reactions have been reported: **Hypersensitivity:** Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred. **Blood:** Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred. **Hepatic and Renal:** Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment. **Gastrointestinal:** Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported. **Other:** Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted. Other reactions have included genital and anal pruritus, genital moniliasis, and vaginitis.

How Supplied: Ancef® (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., or 1 gram of cefazolin; in "Piggyback" Vials for intravenous admixture equivalent to 500 mg. or 1 gram of cefazolin; and in Pharmacy Bulk Vials equivalent to 5 grams or 10 grams of cefazolin.

Smith Kline &French Laboratories
Philadelphia, Pa.

SK&F
a SmithKline company

It's a matter of taste



...and nutrition

Sustacal®

Great tasting nutritional support in a small, easily-consumed serving.

When surgery, therapy or disease reduces your patients' appetites or increases their needs, they need a nutritional boost. They need Sustacal.

Sustacal is a great-tasting nutritional supplement that helps insure daily nutritional needs are met — without replacing the foods patients are eating.

Sustacal is a delicious way to give your patients well-balanced nutrition in a small, easily-consumed serving . . . a maximum amount of nutrition in a minimum volume.

Sustacal comes in a variety of flavors and forms . . . ready-to-use liquid, pudding, and powder that mixes readily with milk.

So, when your patients need extra nutrition, specify Sustacal.

Mead Johnson
NUTRITIONAL DIVISION

© [illegible] Mead Johnson & Company, Evansville, Indiana 47721

Vasodilator Effects of the Sodium Acetate in Pooled Protein Fraction

GORDON N. OLINGER, M.D., PAUL H. WERNER, M.D., LAWRENCE I. BONCHEK, M.D.,
LAWRENCE E. BOERBOOM, PH.D.

Paradoxical hypotension during rapid infusion of plasma protein fraction (PPF) has been attributed to vasodilation by bradykinin in PPF. This study employed a canine, controlled right heart bypass preparation to assess changes in systemic vascular resistance and venous capacitance during infusion of PPF and other possibly vasoactive mediators. Plasma protein fraction caused consistent vasodilation, whereas purified human albumin did not. This vasodilation could be ascribed entirely to acetate, present in PPF as a buffer. Bradykinin in PPF had no effect during venous infusion. Acetate is used widely as a buffer in intravenous and dialysate solutions. Its vasoactive properties must be recognized when such solutions are administered to patients with limited capacity to compensate for sudden vasodilation.

PARADOXICAL HYPOTENSION during rapid administration of human plasma protein fraction (PPF) was reported preliminary by Harrison et al. in Australia in 1971.[11] Torda et al.,[18] as well as Bland and co-workers[4] in this country, confirmed and expanded these observations in 1973. Some of the reported reactions occurred during cardiopulmonary bypass, when PPF was infused into the extracorporeal circuit. Other reactions, however, were documented during venous infusion in patients with intact circulation. A fall in systemic vascular resistance was documented in both circumstances. Vasoactive amines, most specifically bradykinin, were known to be present in PPF, and on the basis of both direct and indirect evidence[13] they were soon implicated as the possible vasodilator elements. Since bradykinin was known to be inactivated within the pulmonary capillary bed[6] and because sensitivity to PPF had been thought by some to be greater during arterial infusion, it was recommended by manufacturers that PPF be given only into the systemic venous system, presumably to obviate the adverse effects of bradykinin.[1]

From the Department of Cardiothoracic Surgery, The Medical College of Wisconsin, Milwaukee, Wisconsin

Despite this counsel, paradoxical hypotension during venous infusion continued to be reported.[12] During these several years, we also observed numerous incidents in which hypovolemic, hypotensive patients monitored on-line for systemic arterial, central venous and left atrial pressures not only failed to respond to rapid venous PPF infusion with increased ventricular filling pressures but often developed further hypotension that was reversible within minutes after PPF infusion was stopped. We remained convinced that either bradykinin inactivation by the lungs was inadequate or that something else in PPF was pharmacologically active as a vasodilator.

Coincidentally, at about the time that we took our clinical observations to the laboratory, attention was being focused nationally on bradykinin and on the even more severe vasodilator effects of prekallikrein activator (PKA), a substance that appeared in a PPF solution developed in 1976 that was marketed as being low in bradykinin and thus purportedly free of vasodilators.[2,7] We employed a controlled whole animal preparation to quantify the vasodilation that occurs with PPF infusion and to delineate the causative factors.

Methods

Experimental Preparation

Mongrel dogs weighing 15–20 kg were anesthetized with intravenous chloralose-urethane and ventilated via an endotracheal tube with a volume ventilator. Splenectomy was done to eliminate changes in blood volume due to splenic contraction. The heart was exposed through median sternotomy. Mean and phasic central aortic (AoP), central venous (CVP) and left atrial pressures (LAP) were monitored directly by

---

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

Reprint requests: Gordon N. Olinger, M.D., Associate Professor, Department of Cardiothoracic Surgery, The Medical College of Wisconsin, 8700 W. Wisconsin Avenue, Milwaukee, Wisconsin 53226.

0003-4932/79/0900/0305 $00.85 © J. B. Lippincott Company

semirigid catheters connected to Statham P23Db transducers. The first derivative of left ventricular pressure (dP/dt) was derived electronically from the pressure signal obtained with a short, rigid catheter inserted through the ventricular apex and connected to a Statham P-50 transducer. Pressure data and electrocardiogram were recorded continuously on a Hewlett Packard 7700 writer. Heparin (3 mg/kg) was given intravenously. Superior and inferior venae cavae and right ventricle were cannulated for venous return into a cardiotomy reservoir connected in series with a stainless steel heat exchanger (to maintain rectal temperature of 37°), a separate calibrated reservoir and a roller pump. A cannulating Micron flow probe inserted in the bypass circuit between roller pump and animal and connected to a Narcomatic RT-500 flowmeter permitted continuous assessment of the constancy of cardiac output (CO) delivered by the roller pump. The pulmonary artery was ligated, and blood was returned by flexible cannula either into the main pulmonary artery (prepulmonary) or, when bypass of the lungs was employed, into the left atrium (postpulmonary). For studies in which postpulmonary return was evaluated, a disposable oxygenator with integral heat exchanger (Bentley Q-100) replaced the cardiotomy reservoir and stainless steel heat exchanger. An infusion port for administration of test solutions was placed in the circuit between the reservoir and the roller pump so that addition of solutions did not effect CO. Changes in venous capacitance were assessed by volume changes in the calibrated reservoir as these related to baseline volume plus the volume of test solutions added to the system. The extracorporeal circuit was primed with heparinized fresh, homologous blood in which pH had been adjusted to 7.4 ± 0.1 by addition of $NaHCO_3$. Right heart bypass was established with constant CO of 80–100 cc/kg/min and with maintenance of normal baseline AoP. Arterial pH, P_{CO_2} and P_{O_2} were monitored throughout the procedure and adjusted as necessary with either the ventilator or $NaHCO_3$.

After at least 5 min of stable control hemodynamics, test solutions were administered over 2½ min with at least 10 min allowed for recovery to control values in each instance. All data were collected at 30-sec intervals. Left ventricular contractility was assessed by observation of LAP, dP/dt and $dP/dt \times P^{-1}$ at a common ventricular pressure of 40 mm Hg. Venous capacitance was assessed as noted, and total systemic resistance (TSR) was calculated from the formula

$$TSR = \frac{AoP - CVP}{CO}$$

Evaluation of Individual Solutions

Phase 1. The first series of experiments in ten dogs was designed to test whether in this preparation prepulmonary infusion of 5% PPF at rates corresponding to clinical volume replacement for hypovolemic shock caused vasodilation similar to that observed clinically. Infusion of 5% human albumin (HA_5) and 25% human albumin (HA_{25}), both known to be free of bradykinin, were also infused for comparison. To avoid vasodilation due to hemodilution, homologous red cells were added to each solution to achieve an hematocrit of 40%. pH was adjusted as necessary to 7.4 ± 0.1 with $NaHCO_3$. Twenty-five per cent human albumin was made isoncotic by dilution with a balanced crystalloid solution, Plasma-Lyte 148®.* Solutions were administered at 5 cc/kg/min (3 cc/kg/min of the colloidal component).

Phase 2. The second series of experiments expanded upon observations made in Phase 1. It was designed to elucidate the vasoactive component or components responsible for Phase 1 observations and to compare postpulmonary infusion of some of the test solutions to prepulmonary infusion. The colloidal solutions in question were prepared with red cells as before, as were several crystalloid solutions containing various concentrations of possibly vasoactive agents. Rates of administration were the same as in Phase 1 studies.

The number of dogs evaluated varied among the test solutions in Phase 2, testing being limited for some solutions by the small supply of specially prepared material available to us. Assays of the activity of bradykinin and of PKA used in test solutions were done independently by Cutter Laboratories, Inc., using techniques described previously.[1,5]

Test solutions. The constituents of all test solutions are summarized in Table 1. Solutions A and H are stock commercial PPF of different manufacturing lots, A being that marketed in January 1977 and H in June 1978. Solution B is stock HA_5, and Solution C is stock HA_{25} diluted with Plasma-Lyte 148. Solution D is stock Plasma-Lyte 148. Solution E is stock HA_{25} diluted with normal saline. Solution F is normal saline with sodium acetate added to achieve an acetate (Ac) concentration similar to that of stock PPF (A and H), 16.8 mEq/l, and G is normal saline with Ac in a concentration similar to that of experimental PPF (I), 4.7 mEq/l. Solution I is experimental PPF low in Ac and without measurable bradykinin or PKA; Solution J is Solution I to which exogenous bradykinin has been added to

---

*Travenol Laboratories, Inc., Deerfield, Illinois.

TABLE 1. *Constituents of Test Solutions*

Solution	Crystalloid	Protein Content (%)	Bradykinin (ng/ml)	Acetate (mEq/liter)	PKA (mUnits/ml)	No. Animals Prepulmonary Infusion
Phase 1						
A—Stock PPF (lot M6479)	None	5	17.0	16.8	<2	10
B—Stock HA_5 (lot M6420)	None	5	<2	6.6	<2	10
C—Stock HA_{25} (lot M6327)	Plasma-$Lyte_{148}$	5	<2	27.0	<2	6
Phase 2						
D—Plasma-$Lyte_{148}$	Plasma-$Lyte_{148}$	0	0	27.0	0	10
E—Stock HA_{25} (lot M6327)	Normal saline	5	<2	<2.0	<2	4
F—Acetate 16.8	Normal saline	0	0	16.8	0	8
G—Acetate 4.7	Normal saline	0	0	4.7	0	4
H—Stock PPF (lot C2068)	None	5	10.8	16.8	4	5
I—Exper. PPF (1937-57)	None	5	<4	4.7	<1	4
J—Exper. PPF (1937-57) + bradykinin	None	5	10.8	4.7	<1	4
K—Exper. PPF (PR2589)	None	5	<2	4.7	39	9

PPF = plasma protein fraction; HA_5 = human albumin 5%; HA_{25} = human albumin 25%.

achieve a concentration similar to that of stock PPF (H). Solution K is an experimental PPF without measurable bradykinin and low in Ac but containing PKA in a concentration similar to that of solutions discussed by Alving et al.[1] All colloidal solutions, except for stock PPF and HA, were designated experimental and not for use in humans. Colloidal solutions were supplied courtesy of Cutter Laboratories.†

Matched pre- and postpulmonary infusions were done for Solutions H, I and J, those combinations of bradykinin and Ac most likely to demonstrate alteration in vasoreactivity due to pulmonary inactivation of vasoactive amines. Studies were completed for H and J in three dogs and for I in two dogs.

Data analysis. All data were analyzed as per cent of control value with each animal serving as its own control. Student's t-test for paired data was used to assess significance of differences. Data are expressed as value ± standard deviation.

Results

Phase 1 (Table 2)

Prepulmonary infusion of stock PPF (A) caused a consistent decrease in TSR to 91% of control at 1 min and to 83% at end infusion, with persistence of the effect 4 min following termination of infusion. Total systemic resistance returned to control 8 min after end infusion. Stock HA_5 (B) caused no change in TSR. Stock HA_{25} diluted in Plasma-Lyte 148 (C) showed a significant fall in TSR that was analogous to that of PPF (A). None of the solutions caused alterations in the various indicators of ventricular contractility or in venous capacitance. These results have been published previously in preliminary form.[19]

Phase 2 (Table 2)

The unexpected fall in TSR during infusion of HA_{25} in Plasma-Lyte 148 (C), a solution without measurable bradykinin, and the similarity of this change to that seen with PPF (A), prompted examination of Plasma-Lyte. Infusion of Plasma-Lyte 148 (D) alone caused the same type of response seen with HA_{25}

TABLE 2. *Changes in Total Systemic Resistance (TSR) During, at Termination and 4 Minutes After Termination of Prepulmonary Infusion of Possibly Vasoactive Solutions*

	Solutions	TSR (% Control) 60 Sec	150 Sec (End Infusion)	390 Sec
Phase 1				
PPF	A	91 ± 6*	83 ± 6*	93 ± 5†
HA_5	B	99 ± 5	97 ± 5	97 ± 8
HA_{25} + P148	C	94 ± 4†	90 ± 7†	100 ± 2
Phase 2				
P148	D	89 ± 7†	76 ± 9†	88 ± 7†
HA_{25} + NS	E	102 ± 5	101 ± 6	101 ± 6
Ac 16.8	F	92 ± 3*	79 ± 6*	88 ± 4*
Ac 4.7	G	101 ± 4	95 ± 5	96 ± 8
PPF 16.8 + B	H	88 ± 6†	74 ± 9†	84 ± 8
PPF 4.7	I	99 ± 2	102 ± 5	97 ± 3
PPF 4.7 + B	J	99 ± 2	99 ± 5	101 ± 5
PPF_{PKA}	K	100 ± 4	99 ± 4	95 ± 10

PPF = plasma protein fraction; HA_5 = human albumin 5%; HA_{25} = human albumin 25%; P148 = Plasma-Lyte 148; NS = normal saline; Ac = acetate; B = bradykinin; PKA = prekallikrein activator.

* $p < 0.001$, value compared to control.

† $p < 0.02$, value compared to control.

---

† Cutter Laboratories, Inc., Berkeley, California.

in Plasma-Lyte (C); there was no alteration in TSR during infusion of HA_{25} diluted in normal saline (E).

Plasma-Lyte 148 is a balanced electrolyte solution containing Na, K, Mg, Cl and gluconate, with NaAc in a concentration of 27 mEq/l used as a buffer to achieve a pH in the physiological range. Of these constituents, only NaAc proved to be vasoactive in our preparation. Examination of the chemical constituents of PPF (A) revealed that it too contains NaAc. Present as 0.25 g of the trihydrate moiety per 100 ml, the calculated concentration of acetate is 18.3 mEq/l, but the actual concentration apparently varies depending on buffer needs during PPF preparation. Albumin solutions on the other hand contain very little acetate, generally around 5 mEq/l.

This finding caused us to query, first, *whether Ac and not bradykinin could be the principal vasodilator in PPF during prepulmonary infusion* and, second, whether postpulmonary infusions of solutions containing commercial concentrations of Ac and/or bradykinin would alter the responses observed with prepulmonary infusion. To pursue these questions, we requested the cooperation of Cutter Laboratories and obtained several experimental solutions along with the then current commercial lot of PPF, which itself contained 16.8 mEq/l of Ac. These are colloidal solutions H, I, J and K. Control normal saline solutions (F and G) containing the same amounts of Ac present in the experimental colloidal solutions were used as Ac controls.

Prepulmonary infusion of Ac alone in saline at 1.68 mEq/l (F) caused a decrease in TSR to 79% control. Acetate alone in saline at 4.7 mEq/l (G), the lowest concentration of Ac in PPF available to us, had no vasodilator effect. Prepulmonary infusion of the new stock of PPF (H) decreased TSR to 74% of control at end infusion. This change was similar to the decrease to 83% we had seen with the older PPF lot (A), despite lesser bradykinin concentration in the newer solution! This change correlated well with the decrease to 79% found with Ac 16.8 (F). Experimental PPF (I), low in Ac and free of measurable bradykinin, had no effect on TSR. When bradykinin (10.8 ng/ml) was added to PPF (I) to make PPF (J), prepulmonary infusion still failed to affect TSR. Thus, of the vasoactive constituents in the new colloidal solutions, H, I and J, only Ac at 16.8 mEq/l caused vasodilation during prepulmonary infusion.

Prepulmonary infusion of Solution K, high in PKA but low in Ac and free of measurable bradykinin, caused changes in TSR that were completely different in both quality and magnitude from changes observed with Ac. There were no changes in TSR during infusion, but from 4 to 9 min after end infusion, several dogs demonstrated 5–15% decreases in TSR that were progressive and sustained for up to 10 min. The group mean of TSR at 7 min from end infusion was 93 ± 9% of control ($p < 0.05$).

Matched pre- and postpulmonary infusion of Solutions H, I and J (Table 3) were inconclusive regarding the extent of vasodilation from postpulmonary infusion of bradykinin when compared to prepulmonary infusion. A trend, suggesting a propensity to further decrease of TSR beyond what might have been attributed to Ac, was apparent for solution H. Some vasodilation also seemed to occur for Solution J during postpulmonary infusion only. The small number of dogs we were able to study precluded valid statistical analysis.

None of the solutions caused alterations in the various indicators of ventricular contractility or in venous capacitance.

Discussion

This study employed a whole animal preparation designed to reveal changes in systemic vascular resistance and venous capacitance during infusion of volume expanders at rates analogous to those required clinically during rapid expansion of blood volume for hypovolemia. The data obtained strongly corroborated previous clinical observations that rapid venous

TABLE 3. *Changes in Total Systemic Resistance (TSR) During, at Termination and 4 Minutes After Termination of Prepulmonary and Postpulmonary Infusions of Possibly Vasoactive Solutions*

	TSR (% Control)					
	60 Secs		150 Secs (End Infusion)		390 Secs	
Solutions	Pre-pulmonary	Post-pulmonary	Pre-pulmonary	Post-pulmonary	Pre-pulmonary	Post-pulmonary
PPF 16.8 (H)	86 ± 7	80 ± 6	70 ± 8	68 ± 12	86 ± 10	75 ± 8
PPF 4.7 (I)	98 ± 3	96 ± 5	100 ± 5	92 ± 4	94 ± 2	97 ± 3
PPF 4.7 + B (J)	100 ± 2	93 ± 6	101 ± 2	94 ± 5	103 ± 2	101 ± 6

PPF = plasma protein fraction; B = bradykinin.

infusion of commercial PPF consistently causes arteriolar vasodilation with a decrease in TSR that is immediate, progressive during infusion and reversible when infusion is stopped. Human albumin solutions administered in the same preparation have no demonstrable vasoactive properties. As discussed below, the vasodilation observed during venous infusion of commercial PPF solutions in this study could be attributed entirely to acetate.

On the basis of these data we have stressed that PPF not be used for rapid volume expansion but that human albumin solutions be used instead.[19] This stance is consistent with that of other authors[4,7] and with the current recommendations of the major North American PPF manufacturers, whose PPF package inserts interdict arterial infusion and caution against intravenous administration at rates exceeding 10 cc/min, hardly sufficient for treatment of acute hypovolemia. Unfortunately, precedent and inertia have kept PPF solutions on emergency room and intensive care unit shelves, with usage dictated by the acute need for a volume expander without regard to the package insert. This has been true as recently as December 1978 in our own affiliated hospitals.

The larger and more interesting issue raised by this study, however, relates to the etiologic roles of acetate versus bradykinin in the vasodilation observed. Since traditional preparation of PPF solutions has preserved the presence of amines long recognized to be vasoactive and preparation of purified albumin solutions has virtually eliminated these compounds, it had seemed logical to attribute the difference in pharmacological behavior of the two solutions to the presence of such compounds as bradykinin in PPF only. To our knowledge, vasodilation by a nonprotein moiety has never been seriously suggested. A considerable amount of research effort and breast-beating has been generated by concerns about bradykinin. Indeed, PPF solutions were recently developed and marketed with bradykinin reduced to physiological amounts to prevent hypotensive reactions. Unfortunately, these solutions also caused such severe hypotensive reactions that the Food and Drug Administration was prompted to an investigation, and the manufacturers were forced to recall the products. After careful biochemical examination of this new PPF preparation, PKA was implicated as the vasoactive culprit by association.[2] It was notable that many of the reactions attributed to PKA were apparently more delayed in onset and longer in duration than those reported with previous PPF solutions. In the nine dogs we studied with prepulmonary infusion of low Ac, high PKA solution (K), hypotensive reactions were similarly delayed and prolonged but were much less severe, with overall decrease in TSR for the entire group reaching a value of 93% of control 7 min after the end of infusion. This phenomenon has been attributed to *in vivo* activation of the kallikrein system prior to generation of endogenous bradykinin. We feel, however, that the PKA story is clouded by the report to us that the PKA solutions studied by Alving et al. contained from 10 to 60 mEq/l of Ac, mostly in the range 10–20 mEq/l.[8] We do not know the correlation of Ac level with severity of clinical reaction, but it is possible that acetate in those solutions might have acted synergistically with PKA to provoke marked hypotension. The PKA problem has subsequently forced a return to PPF solutions containing higher concentration of bradykinin. Concern, therefore, over potential vasodilator properties of bradykinin in PPF has persisted.

Our study casts doubt on the concept that bradykinin was ever highly instrumental in causing hypotension during *venous* infusion of PPF. Rather, we infer from our data that Ac, which to our knowledge has been present at >15 mEq/l in every PPF solution marketed since the late 1960s (stable plasma protein solution produced in Australia may be an exception[17]) and has never been present at >6 mEq/l in purified albumin solutions, has vasoactive properties that make it likely to be a primary cause of the hypotensive reactions reported clinically. We found that Ac was the vasoactive ingredient in Plasma-Lyte 148 (used initially in our study to dilute HA_{25}). Infusion of Ac alone in the concentration present in the commercial PPF solutions (A and H), that is, 16.8 mEq/l, resulted in a decrease in TSR virtually indentical to that observed with infusion of either of the two commercial PPF solutions, each of which also contained bradykinin. When Ac in saline was reduced in concentration to 4.7 mEq/l, no significant change in TSR occurred. The availability of a small quantity of experimental PPF solution low in Ac, 4.7 mEq/l, and free of measurable bradykinin (Solution I) enabled us to examine bradykinin in PPF independent of Ac. Prepulmonary infusion of Solution I caused no change in TSR; moreover, when a commercial concentration of bradykinin was added to this low Ac PPF (to make Solution J), prepulmonary infusion still had no effect. *The vasodilation observed during venous infusion of commercial PPF solutions in this preparation could be ascribed entirely to acetate.*

Bradykinin may have had additional vasoactive effect when we infused Solutions H and J into the arterial side of the circulation. Such a finding would be consistent with the concept that pulmonary inactivation of bradykinin can be adequate only for venous infusion and would support the interdiction of PPF for arterial infusion. Unfortunately, the number of animals we were able to study successfully with matched pre- and postpulmonary infusion was too small to provide statistical confirmation of what appeared to be a consistent trend. Further evaluation of pre- and postpulmonary administration of various doses of bradykinin is pending.

Our discovery of the vasoactive role of Ac in PPF came at a time when the attention of others was being focused on the vasoactive properties of Ac used in hemodialysate solutions. We did not know that Ac and other Krebs cycle intermediates had been evaluated as far back as 1962.[15] In 1965, Frohlich showed that in an isolated limb preparation Ac was a potent arteriolar vasodilator with what appeared to be a direct local effect on vascular smooth muscle.[9] He hypothesized that the mechanism of this effect might be local Ca^{++} binding, but further elucidation of the mechanism is still forthcoming. Nonetheless, since Ac is readily metabolized to CO_2 and H_2O and its Ca and Mg salts are highly soluble, it became an appealing alternate to bicarbonate as a buffer in hemodialysis solutions. Acetate in dialysates soon became standard, and it was well tolerated by patients despite its vasoactive potential until the utilization of large surface, high efficiency dialyzers increased the rapidity of Ac exchange. In the past 3 years, several clinical and laboratory studies have appeared in the dialysis literature showing that acetate dialysis consistently causes systemic vasodilation and that in certain patients it provokes episodes of severe hypotension.[3,10,14,16] Patients most prone to adverse effects seem to be those with preexisting cardiac insufficiency and diminished cardiovascular reserve. As suggested by Novello et al.,[16] Ac intolerance may occur by one or more of three mechanisms: 1) excessive rate of administration of exogenous Ac, 2) circulatory insufficiency with decreased delivery of Ac *in vivo* to metabolic sites such as liver and 3) decreased metabolic capability, such as in hepatic insufficiency. Any of these mechanisms in a patient unable to increase cardiac output in response to peripheral vasodilation will facilitate a hypotensive reaction.

These concurrent but independent dialysis studies substantiate our assertion that Ac is a causative factor in PPF hypotensive reactions and help to illuminate a still larger problem. Acetate is not restricted to dialysates and PPF. It is also a standard buffer in newer crystalloid solutions such as Plasma-Lyte 148 and Normosol R®‡ that are designed to provide physiological pH. Such solutions are becoming more popular for routine intravenous therapy, for crystalloid oxygenator primes during cardiopulmonary bypass and for resuscitation from hypovolemia. The potential for unsuspected adverse reactions is considerable whenever solutions containing Ac in the range of 15–20 or more mEq/l are to be administered rapidly. In this circumstance, recognition must be given to the vasoactive properties of Ac and to the ability of the patient to compensate for sudden vasodilation. We feel such solutions are contraindicated in the critically ill, hypotensive, vasoconstricted patient, particularly when there is diminished cardiac reserve. If Ac-containing solutions are being infused and hypotension occurs or fails to be corrected in the patient previously in shock, the infusion should be stopped promptly, and other volume expanders given instead. The threat of Ac "toxicity" in this context is that continued hypotension will be ascribed inappropriately to another cause and that a potentially correctable problem may remain uncorrected.

References

1. Akin, G. M.: Memorandum to Field Sales Management and Sales Force. Cutter Laboratories, July 1973.
2. Alving, B. M., Hojima, Y., Pisano, J. J. et al.: Hypotension Associated with Prekallikrein Activator (Hageman-factor Fragments) in Plasma Protein Fraction. N. Engl. J. Med., 299:66, 1978.
3. Arzawa, Y., Ohmori, T., Imai, K. et al.: Depressant Action of Acetate upon the Human Cardiovascular System. Clin. Nephrol., 8:477, 1977.
4. Bland, J. H. L., Laver, M. B. and Lowenstein, E.: Vasodilator Effect of Commercial 5% Plasma Protein Fraction Solutions. JAMA, 224:1721, 1973.
5. Brocklehurst, W. E.: Assay of mediators in hypersensitivity reactions. *In* Weir, D. M. (ed.): Handbook of Experimental Immunology. Philadelphia, F. A. Davis, 1967. pp. 1159–1162.
6. Colman, R. W.: The Human Plasma Kallikrein-kinin System. Prog. Hematol., 7:255, 1971.
7. Colman, R. W.: Paradoxical Hypotension After Volume Expansion with Plasma Protein Fraction. N. Engl. J. Med., 299:97, 1978.
8. Fournel, M. A.: personal communication. Cutter Laboratories, March 1979.
9. Frohlich, E. D.: Vascular Effects of the Krebs Intermediate Metabolites. Am J. Physiol., 208:149, 1965.
10. Graefe, U., Milutinovich, J., Follette, W. C. et al.: Less Dialysis-induced Morbidity and Vascular Instability with Bicarbonate Dialysate. Ann. Intern. Med., 88:332, 1978.
11. Harrison, G. A., Robinson M., Stacey, R. V. et al.: Hypotensive Effects of Stable Plasma Protein Solution (SPPS): A Preliminary Communication. Med. J. Aust., 2:1040, 1971.
12. Isbister, J. P. and Biggs, J. C.: Reactions to Rapid Infusion of Stable Plasma Protein Solution During Large Volume Plasma Exchange. Anaesth. Intensive Care, 4:105, 1976.
13. Izaka, K., Tsutsui, E., Mima, Y. and Hasegawa, E.: A Bradykinin-like Substance in Heat-treated Human Plasma Protein Solution. Transfusion, 14:242, 1974.
14. Kirkendol, P. L., Robie, N. W., Gonzalez, F. M. and Devia, C. J.: Cardiac and Vascular Effects of Infused Sodium Acetate in Dogs. Trans. Am. Soc. Artif. Intern. Organs, 24:714, 1978.
15. Molnar, J. E., Scott, J. B., Frohlich, E. D. and Haddy, F. J.: Local Effects of Various Anions and H^+ on Dog Limb and Coronary Vascular Resistances. Am. J. Physiol., 203:125, 1962.
16. Novello, A., Kelsch, R. C. and Easterling, R. E.: Acetate Intolerance During Hemodialysis. Clin. Nephrol., 5:29, 1976.
17. Schiff, P.: personal communication, Commonwealth Serum Laboratories, April 1979.
18. Torda, T. A., Harrison, G. A., McCulloch, G. H. et al.: Circulatory Effects of Stable Plasma Protein Solution (SPPS). Med. J. Aust., 1:798, 1973.
19. Werner, P. H., Boerboom, L. E., Bonchek, L. I. and Olinger, G. N.: Hemodynamic Response to Rapidly Infused Protein Volume Expanders. Surg. Forum, 29:34, 1978.

---

‡ Abbott Laboratories, N. Chicago, Illinois.

DISCUSSION

DR. JOHN A. COLLINS (Stanford, California): As the authors have indicated, this material is now being looked at very hard, particularly in the dialysis solutions, where the amount that is given exceeds even the amount that is usually given in conjunction with Plasmanate. Indeed, there may be not only vasoactive but certain metabolic changes that are detrimental to the patient.

I would like to focus on the other part of the problem, that is, the part that deals with the PKA, or the bradykinin, or whatever else it is that might be in this solution that's causing trouble. I am not sure that the authors have established that there is not something else in addition to the acetate that has caused the difficulty.

The reason I say that is based on very soft data. A regulatory agency often has to work with soft data if there is a question of public safety and public good. I am not speaking officially now, but I have to point out that I was a member of the FDA panel which dealt with this question, and which withdrew certain lots of Plasmanate from the market. At the time (and even now in retrospect) the evidence in favor of something other than acetate in the solutions was, indeed, very compelling, although again I must acknowledge that it was soft.

There was clearly a marked cluster of deaths and serious reactions suddenly reported from various sources, associated with the use of Plasmanate. The FDA attempted to backcheck by doing a random sort of telephone interview of various institutions, including the ones that had reported difficulty, calling different people in that institution, and institutions that had not reported any difficulty. It turned up disturbing incidence of unreported serious reactions.

What was striking about this data is that it related only to certain lots of Plasmanate and not to all lots. That's where the question of cause really comes up, because all the lots of Plasmanate contained the same acetate content, but it was only certain peculiar lots that were associated with this apparently sudden increase in serious reactions.

One other line of evidence made this a fairly compelling argument. Those very lots of Plasmanate that turned out to be producing these serious reactions were lots that had been produced by a special method. The manufacturer, responding to the concerns about the levels of bradykinin in the material, changed the manufacturing process, and, indeed, got rid of bradykinin. In so doing, however, the manufacturer made the problem much worse than it had been.

It turns out, ironically, that bradykinin is probably a fairly benign material that does not cause much difficulty in the amount that was being infused into most patients. Whatever was done with the manufacturing process produced something else, which, based on the soft data, looked to be potentially extremely dangerous, and therefore the material was withdrawn from the market.

Now, the detective work currently points toward prekallikrein activator (PKA), but that by no means is a proven association. Trying to pinpoint what it is in this material that caused the difficulty has been a difficult job. I recommend the proceedings of a workshop held by the FDA with all the interested parties, including the manufacturer and investigators in the area. This workshop will be published soon.

Some of the things that came out of this workshop, however, are worth noting here. First of all, it is extremely difficult in biologic models to reproduce whatever it was that was happening in patients. The models that were finally used were complex. Not just intact animals were used; the animals had to be modified in certain ways, and it worked only with certain species. In other words, whatever is in the material is difficult to identify with a bioassay.

Secondly, the investigative work that was done indicated that there may well be marked species differences in the response to this material, so I am not sure that being unable to show an effect in dogs carries over to prove that something does not exist for man.

Third, the clinical evidence indicated, as the authors have also indicated, that these reactions were seen mostly in critically ill patients, and, indeed, they tended to occur mostly in patients who were either on cardiopulmonary bypass or who were undergoing acute hemodialysis, but not chronic hemodialysis; they were undergoing dialysis for acute renal failure, with other complicating factors also present.

Whatever it is that was in this material that was causing the difficulty may, in fact, not even be manifest in patients who have intact defenses, but it may be manifest primarily in people who have already undergone a pretty extensive systemic inflammatory reaction.

With those concerns, I have one question for the authors. Where did you get the material that had the high PKA-level? Did this come from the manufacturer? Was this one of the lots that was implicated in reactions in humans? If it was, did you modify it in any way before you tested it?

DR. G. N. OLINGER (Closing discussion): Dr. Collins, your suggestion and that of the group that investigated the high PKA solutions that there may be something else going on in those particular solutions is of interest not only from the human data, but from our own animal data. In the dogs we studied with these solutions, we found a highly variable response.

Indeed, in two of the dogs there was a complete failure to recover vasoactive tone during the study, whereas in other animals there appeared to be very little response. We have been unable to determine what it is that makes one animal different from the other.

To answer your question regarding that material, it was provided to us by Cutter Laboratories, purely out of response to our questions. They were good enough to provide material to our specifications out of their experimental lots. I don't think the material that we obtained, high in PKA, was the same material that was used clinically because our solution was low in acetate, whereas most of the clinical material contained acetate in concentrations between 10 and 20 mEq/l and, as I have mentioned, as high as 60 mEq/l.

We agree that bradykinin is probably a fairly benign agent as long as it is infused on the right side of the circulation. However, when it is infused on the left side of the circulation, it is a potent vasodilator. It may act synergistically with whatever it is that causes vasodilation in response to acetate. The exact mechanism of acetate vasodilation, to my knowledge, is still not well known. It is purely a local effect on smooth muscle.

The acute renal failure patient is one that I think is particularly prone to the effects of Plasmanate, or PPF solutions, as well as to acetate. Patients critically ill with acute renal failure, particularly when limitation of cardiac output has contributed to renal failure, must be watched carefully to assure they do not get into further trouble during hemodialysis.

Surgical Treatment of Chronic Pancreatitis

Twenty-two Years' Experience

L. WILLIAM TRAVERSO, M.D., RONALD K. TOMPKINS, M.D., PAUL T. URREA, B.A., WILLIAM P. LONGMIRE, JR., M.D.

From the Department of Surgery,
UCLA School of Medicine,
Los Angeles, California

Seventy-four patients underwent operation for chronic pancreatitis during a 22 year period at UCLA Hospital. Follow-up data obtained for 60% of these patients an average of 3.2 years postoperation were analyzed by computer for statistically significant benefit between paired operation combinations and the variables of pain relief, stool habits, alcohol use, readmission for pancreatitis, and narcotic use. The combined group of total and cephalic pancreaticoduodenectomy proved more effective with respect to pain relief and readmission ($p < 0.05$) than the group that had pseudocyst drainage. The comparison of groups that underwent resection or ductal drainage showed no statistical differences for the above variables. Regardless of type of operation, if the patient had evidence of pancreatic calcifications and had abstained from alcohol postoperatively, the likelihood of a return to normal activity was more favorable ($p < 0.05$).

THE NATURAL HISTORY of chronic pancreatitis includes a broad spectrum of variables, making treatment decisions difficult. As Spiro states, "We know its associations, we can chart its course, but we know little more."[11] The difficulty is further compounded by the paucity of reports concerning various drainage and resection techniques from relatively few medical centers. While abdominal pain is the typical chief complaint and surgical treatment achieves some benefit in the majority of cases, the kind of operation that provides symptomatic relief for each type and stage of chronic pancreatitis is unclear. With or without treatment, all patients who have smoldering chronic pancreatitis ultimately suffer from progressive exocrine insufficiency and diabetes. During the past 22 years we have developed a plan of surgical treatment aimed at relieving abdominal pain based on the degree of parenchymal inflammation, fibrosis and calcification, as well as the condition of the major ductal system. Although previous reports on the treatment of chronic pancreatitis have yielded considerable data, an in-depth computer analysis of our surgically treated cases might provide further insight into the management of this puzzling disease.

Patients and Methods

Between 1955 and 1977, 419 patients were admitted to UCLA Hospital with a diagnosis of pancreatitis. After reviewing their charts, 279 patients who were identified as having a definite diagnosis of pancreatitis were divided into two groups: acute (22%) and chronic (78%), in accordance with the Marseilles Classification.[7] The etiology, frequency, average age, and male:female ratio for the total group and subgroups are listed in Table 1. The high percentage of chronic patients may reflect the referral pattern of admissions to our hospital. In the operated cases there was a positive correlation with alcohol use (65%) and a negligible incidence of associated biliary tract disease (8%). Although miscellaneous causes of the disease (28% in our series) were usually unknown, they were probably associated with unverified alcoholic intake, rather than stemming from nonpenetrating pancreatic trauma, hyperparathyroidism, hyperlipidemia, or familial pancreatitis. During their hospitalization, 27% of the total group underwent operations for pancreatitis and were diagnosed as having long-standing pancreatitis verified at laparotomy. The specific procedures utilized are listed in Table 2.

The predominant indication for operation was abdominal pain (continuous in half of our patients), followed by the necessity for pseudocyst drainage in 26%, although most of the latter also complained of abdominal pain. Charts of the patients who underwent operation were reviewed in detail for 261 variables in their past medical history, physical examination,

---

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

0003-4932/79/0900/0312 $00.90 © J. B. Lippincott Company

TABLE 1. *Pancreatitis Characteristics*

	Number of Patients			
	279	62	217	74
	Per Cent Total	Per Cent Acute	Per Cent Chronic	Per Cent O.R.
Alcohol	64	34	73	65
Biliary	8	19	5	8
Other	28	47	22	27
Avg. age in yrs.	45	38	47	45
Male:Female	1:1	1:2	1:1	1:1

TABLE 2. *The Pancreatic Operations Performed on 74 Patients*

Pseudocyst drainage		19 (26%)
Drainage		24 (32%)
Lateral	(9)	
Distal	(3)	
Sphincteroplasty alone	(12)	
Biliary bypass		3 (4%)
Resection		28 (38%)
Whipple	(5)	
Total	(8)	
Distal (40–80%)	(7)	
(95%)	(8)	

laboratory studies, and operations performed. Followup information was obtained by using a ten-part questionnaire to indicate postoperative time, abdominal pain, pain medications, alcohol use, appetite, weight, strength, bowel habits, insulin or pancreatic enzymes, and activity or work status. There were 52 variables among the ten categories. A total of 18,792 variables were computer analyzed for frequency. All paired-operation combinations were compared by Chi-square analysis by using the frequency of each variable as listed in Table 3. In addition, all postoperative patients were divided into groups according to the presence of radiographic calcifications or continued use of any amount of alcohol. These groups were then compared to the variables shown in Table 3 via Chi-square analysis.

Preoperative Evaluation

The etiology, average age, and male:female ratio of the *operated subgroup* are listed in Table 1. In only 8% was the source considered to be cholelithiasis. Alcohol had been used excessively in the past by 65%, the usual intake being more than four drinks of liquor every day. Although most patients in our series had stopped drinking when first seen, they claimed to have taken their last drink an average of 3.6 years (range 0.18 to 19 years) prior to UCLA Hospital admission. Previous reports in this country and in France also reflect a high incidence of alcohol use—58%,[16] 61%,[3] 62.7%,[17] and 78.5%.[2] In Japan, however, the incidence of alcoholism is lower (30%) and cholelithiasis is likewise infrequent (11%).[10] The 1:1 male:female ratio in our series was similar to the findings of Way et al.,[16] possibly reflecting the social use of alcohol in the United States rather than in France[3] or in Japan,[10] where the ratio is 2:1.

The chief complaint of 94% was pain that began an average 5.6 years prior to admission (range, one month to 35 years). Located in the epigastrium (78%) or back (65%), the pain was described as continuous (chronic pancreatitis) in half of the cases, and intermittent (chronic relapsing pancreatitis) in the other 50%. By the time of admission the average frequency of acute pancreatitic episodes was every 5.3 months, associated with a high serum amylase in 78% and with alcohol usage in 57% of cases. These exacerbated episodes of pancreatitis had required an average of three hospitalizations before admission to UCLA Hospital. A majority of patients (63%) were taking pain medication at admission; 25% were using codeine or Talwin®, and another 25% were getting Demerol® or morphine by injection or by mouth.

The majority (79%) denied steatorrhea, and only 15% were taking pancreatic enzyme supplements at the time of admission. One-fourth were diabetic, 11% were receiving insulin. The average weight loss since the beginning of illness was 19% of total body weight. Previous pancreatic surgery had been performed on 17%, half of which were pseudocyst drainage procedures. Other major operations, primarily cholecystectomy, had been performed on 49%.

The physical examination was unremarkable except that 48% of patients were thin or cachectic, and 66% evidenced palpable abdominal tenderness or an abdominal mass. Abdominal rigidity or rebound was rarely evident. Admission laboratory studies showed a normal hematocrit, white blood cell count, and platelet count in most patients; 42% had a prolonged prothrombin time associated with a normal partial thromboplastin time. Urine amylase was elevated in 22%, while serum amylase exceeded 200 Somogyi units per deciliter in 37% of patients. Except for serum amylase, the most frequently elevated blood chemistry values were alkaline phosphatase (39%) and fasting blood

TABLE 3. *Outline of Statistical Analysis*

Operation	Variables
Pseudocyst drainage	Narcotics
Ductal drainage—all	Loose stools
lateral drainage	Activity
Resections—all	Pain ↓
Whipple and totals	Readmits
Whipple only	
Totals only	
Distal resections	

TABLE 4. *Follow-up Results (44 Patients)*

Time postop	3.2 yr (.08–12)
Pain decreased or absent	76%
Narcotics	43
Alcohol	36
Insulin (avg. 32 nph units)	30
Pancreatic enzymes	52
Normal activity	80
Gained weight	70

sugar (22%). Preoperative x-ray studies showed pancreatic calcifications in 39% of patients, but in the 41 upper GI series obtained, the typical finding was anterior displacement of the stomach. An ultrasound was performed in 35% of cases; half of these revealed pseudocysts, 88% of which were single, and 75% located in the pancreatic head or neck. The pancreas was enlarged in 52% of cases. ERCP performed in 19% of patients achieved a 64% cannulation rate, and of these, 90% were abnormal. Intraoperative cholangiograms were performed in 29 patients, with 45% showing intrapancreatic bile duct stenosis (18% of the entire surgical group).

Operative Results

Types of operations were equally divided among three categories (Table 2): pseudocyst drainage, ductal drainage, and parenchymal resection. Three patients underwent a choledochojejunostomy only. There were no intraoperative deaths. The 30 day postoperative death rate was 7%, owing to an uncontrolled bleeding ulcer and hepatic failure in one patient each, and myocardial infarction or arrhythmia in three patients undergoing the following operations: pancreaticojejunostomy, cystduodenostomy, total pancreatectomy, 40% distal resection, and 95% distal resection. Major postoperative complications occurred in 11% of cases of which pneumonia occurred in 3%, pulmonary embolus in 1%, myocardial infarction in 3%, and wound infection in 4%.

By the time of discharge no patient was taking Demerol or morphine, 31% were receiving insulin, and 81% claimed that their pain had decreased or totally disappeared. Follow-up data obtained from 44 patients an average of three years postoperatively are listed in Table 4. Chi-square analysis of these data indicated no statistically significant difference among the three basic operations or subgroups as listed in Table 3. The subgroup that underwent combined Whipple and total pancreaticoduodenectomy, however, proved to be statistically superior to the group that had pseudocyst drainage in two respects: decreased or absent abdominal pain ($p = 0.05$) and fewer readmissions for recurrent pancreatitis ($p = 0.03$). In comparing the results of these various procedures, it must be remembered that specific operations were selected for specific pathological conditions of the pancreas and the three operative procedures are not necessarily interchangeable nor comparable. For example, a pancreatic resection may have been selected as the treatment of choice for an individual who did not have a pseudocyst suitable for drainage nor a duct sufficiently dilated to be utilized for duct enteric drainage. In general, excisional therapy was utilized for cases with the most severe and extensive pathological changes. Regardless of operation type there was a favorable result and a return to normal activity if the patient had pancreatic calcifications or did not resume use of any quantity of alcohol (Table 5). The other variables in Table 3 were not significantly related to calcifications or alcohol.

Discussion

Preoperative data were remarkably similar to findings in other reports (Table 6), re-emphasizing the fact that we know the associations of chronic pancreatitis and can chart its course.

Our typical patient was severely incapacitated by persistent or recurrent abdominal pain for which pain medication was regularly utilized. Multiple previous hospital admissions had been required during exacerbation of symptoms approximately every five months. Half of our patients were taking narcotics when first seen. Most had stopped drinking prior to admission (average of three and a half years), but had substituted narcotics for liquor. The alcohol history among the majority included at least three hard liquor drinks per day. A small percentage presented with signs and symptoms suggestive of pancreatic endocrine (25%) or exocrine (21%) insufficiency. Loss of appetite combined with some degree of malabsorption may have played a role in the 42% incidence of a prolonged prothrombin time. However, a liver etiology might also be implicated despite the low reported correlation of cirrhosis and chronic pancreatitis. The 39% incidence of elevated serum alkaline phosphatase levels may be an indication of intrapancreatic biliary stenosis; in our series, progressive pancreatic fibrosis in chronic pancreatitis accounted for an 18% cholangiographic incidence of biliary stenosis and in another series documented by ERCP, the figure was 14%.[4]

TABLE 5. *Per Cent Regaining Normal Activity*

Normal Activity	Yes	No	p
Calcifications	73%	27%	0.047
No alcohol	82%	18%	0.041

TABLE 6. *Surgical Treatment of Chronic Pancreatitis—22 Years' Experience Comparison between Series*

Report	No. of Cases	M	F	Mean Age	Calcific	Alcoholism	Cysts	Diabetes	Steatorrhea
Way et al.[16]	57	30	27	42	42.1% (24)	57.9% (33)	28.1% (16)	33.3% (19)	24.6% (14)
Leger et al.[3]	148	135	13	39.8	69.6% (103)	61.5% (91)	19.6% (29)	12.8% (19)	31.8% (47)
Frey et al.[2]	149	101	48	40	48.3% (72)	78.5% (117)	42.3% (63)	26.2% (39)	6.7% (10)
Sato et al.[10]	71	48	23	45.5	56.3% (40)	29.6% (21)	22.5% (16)	29.6% (21)	9.9% (7)
White et al.[17]	142	83	59	43.7	34.5% (49)	62.7% (89)	28.9% (41)	19.0% (27)	16.9% (24)
UCLA Series	74	39	35	44.4	39.2% (29)	64.9% (48)	32.4% (24)	24.3% (18)	27.0% (20)
Total	641	436 (68.0%)	205 (32.0%)	42.1	49.5% (317)	62.2% (399)	29.5% (189)	22.3% (143)	19.0% (122)

Recent studies[5,8,9] propose that persistent alcoholic intake of an unspecified amount over a period of months or years produces a hypersecretory state of pancreatic parenchymal cells with a spotty distribution of intralobular periductal fibrosis and obliteration. Acinar cell hypersecretion of protein is suggested as the initial pathological effect of chronic alcoholic intoxication followed by precipitation of protein plugs in the finer ducts which block the ducts, undergo calcification, and by irritation produce the ductal and lobular lesions of chronic pancreatitis. The involved ducts are irregularly dilated, the epithelium is lost, the periductal connective tissue encroaches on the lumen of the duct to form areas of stenosis, pancreatic cysts, or cause complete disappearance of acini and ducts in the territory drained by a blocked duct. As the disease progresses, these *scattered* areas coalesce to replace pancreatic parenchyma with areas of *sclerotic fibrosis*.

Some speculation is required, however, to progress from this well-conceived and specifically documented explanation of the pathological changes occurring in the smaller ducts to the alternating areas of constriction, dilatation and calculi formation frequently found in the duct of Wirsung in patients suffering from chronic pancreatitis. This theory suggests that small duct fibrosis and reaction may be sufficiently intense at some site adjacent to the main duct to provoke stenosis followed by stasis and precipitation of the protein plugs in the duct of Wirsung which subsequently form calculi, thereby promoting the same reaction around the major duct that has been observed in the lesser secondary ducts.

We have attempted to analyze our results of various types of treatment applied to different pathological changes that may accompany chronic pancreatic disease. Inasmuch as the earliest obstruction usually occurs in the pancreatic head and neck, pancreatic pseudocysts of a few millimeters to 5 cm may frequently develop in this area. In our cases, 75% of pseudocysts located by ultrasound were located in the head or neck of the gland. It is not clear, however, why a few patients with extensive chronic calcifying pancreatitis do not complain of pain. Perhaps pain is produced by obstruction of normal adjacent lobular ducts followed by inflammation and not merely from the presence of fibrosis, duct dilatation and calcification. If one accepts the proposal that the disease process starts in the small ducts and secondarily affects the major duct, it is difficult to explain why extensive drainage of the duct of Wirsung alone provides pain relief. It would appear that the process could only be relieved by excision of that portion of the gland containing the small duct changes. On the other hand, it could be postulated that the frequently occurring small duct disease in the head and neck of the gland produces a secondary stenosis in the proximal portion of the main duct which is then followed by calculus formation and obstruction of the main ductal system in the body and tail. Extensive drainage of this obstructed major duct system could be expected to provide symptomatic relief under these conditions. Our experience leads us to believe that lateral pancreaticojejunostomy is most successful when the duct is incised well down into the head of the gland and out onto the uncinate process. The sphincter of Oddi is then divided through an open duodenostomy, calculi are removed and stenotic areas dilated until there is extensive open drainage laterally into the jejunum and proximally into the duodenum. If adequate drainage cannot be obtained because the ductal system is obliterated by scar or numerous calculi, or if there are persistent subacute inflammatory reactions and multiple pseudocysts in the parenchyma of the gland, a resection is necessary. Indeed, if such changes are present throughout the gland, a total pancreatectomy is required to obtain optimal pain relief. Side-to-side pancreaticojejunostomy has relieved pain more successfully if radiographic pancreatic calcifications are present.[6] The reason is unclear and may possibly be related to the likelihood of a dilated duct when calcifications are present. Our results suggest that all patients, regardless of the type of operation they have, will respond favorably to a pancreatic operation if calcifications are present.

Selection of a particular operation for a specific case was based on the following general principles: large solitary pseudocysts, if attached to the posterior stomach wall, were drained by cystogastrostomy; otherwise, a Roux-en-Y type cystjejunostomy was utilized. Single or multiple small cysts with marked surrounding parenchymal inflammation, a condition typically seen in the head of the gland, were treated by partial pancreatectomy, usually pancreaticoduodenectomy. Pseudocysts that recurred following drainage were treated by partial pancreatectomy.

A sphincteroplasty alone was performed in unusual cases where there was evidence of isolated obstruction at the sphincter of Oddi with uniform diffuse distal duct dilatation, or while searching for the pancreatic duct for a pancreatogram.

The commonly encountered diffusely dilated pancreatic duct with alternating areas of constriction and dilatation (chain of lakes variety) was drained by a lateral pancreaticojejunostomy. We are repeatedly impressed by the observation that persistent inflammation, calcification and duct obstruction in the head of the pancreas serves to initiate and perpetuate inflammatory changes in the more distal portions of the gland, and that symptomatic relief depends on obtaining adequate duct drainage of the head and uncinate portions of the pancreas by widely opening the proximal portion of the duct of Wirsung and the duct to the uncinate process and removing all obstructing calculi or by excision of the involved pancreas by pancreaticoduodenectomy. As a more conservative procedure, this operation was first used even in cases where pancreatic excision might eventually be necessary. Marked parenchymal inflammation with or without small pseudocysts and with extended duct obstruction owing to fibrotic obliteration or impacted calculi was treated by resection of the involved area.

Utilizing these principles and selecting the operative procedure best adapted to the pathological changes in each case as outlined above, lateral pancreaticojejunostomy ductal drainage in our patients provided pain relief as effective as that of the proximal or complete pancreaticoduodenectomy by statistical comparison. Excluding the one death that occurred among the 13 proximal or total pancreatic resections and the one death among the nine extensive side-to-side pancreaticojejunostomies, all of these procedures achieved complete or substantial pain relief. The poor results in the pseudocyst drainage group stem from the fact that only localized drainage of an extensive spotty process was obtained and the progressive natural history of the disease was unchanged. Moreover, the fact that half of the patients had undergone prior pseudocyst drainage procedures before admission to UCLA underscores the temporary relief so frequently accompanying internal pseudocyst drainage in chronic calcific pancreatitis. Frey reports a 31% incidence of reoperation after internal pseudocyst drainage, with a 37.5% reoperation rate for cystgastrostomy.[1] Unless the disease process is confined to the distal portion of the pancreas, a 40–80% distal resection is unlikely to achieve pain relief. An extended resection of 80–95% of the distal gland will remove more of that portion of the pancreas in which the chronic inflammatory changes usually reside and, therefore, the more extensive resections have obtained greater pain relief.[17] However, persistent smoldering pancreatitis and abdominal pain, pancreatic fistulas or bile leak, and subsequent diabetes in 72%[2] have led us away from the 95% distal resection. Instead, we prefer an extended *proximal* 95% resection, leaving the area of the gland with the lowest frequency of pancreatitis and the highest concentration of pancreatic islets. Our experience with pancreaticoduodenectomy or total pancreatectomy has demonstrated complete pain relief in 64% and some relief in the remaining patients, although minimal experience has been reported by others with these extensive resection procedures and do not reflect our favorable results. White et al. report three such patients, all with recurrent symptoms,[17] and Frey et al. reported 19 patients with a 58% incidence of some degree of pain relief commensurate with the 56% rate of pain relief following 80–95% distal pancreatectomy.[2] Many of their patients treated by a Whipple procedure had been lost to followup or had died; possibly the pain relief outcome may have improved in those cases. Leger et al. reported a 50% mortality among 16 patients six years after pancreaticoduodenectomy. Of the remaining survivors, 75% experienced good results.[3]

The assumption has always been that if the patient resumes the use of alcohol, any beneficial effect of an operative procedure will be compromised, and our data statistically confirm this assumption. Indeed, persistent alcohol consumption subsequent to pancreatectomy has proved to be the only significant prognostic factor associated with a limited period of survival.[3] For this reason, the psychosocial adjustment of all patients must be carefully considered before any operation is performed. Extensive resectional procedures should not be contemplated when the patient does not have the intelligence or motivation to cooperate with appropriate dietary and medical management during the remainder of his life. The possibilities of social and employment rehabilitation must also be carefully evaluated as factors affecting the eventual outcome of treatment.

Encouraged by the results of complete or proximal pancreaticoduodenectomy for pain relief, a pylorus preservation modification of the Whipple operation has been performed[13] whereby the side effects of an extensive gastric resection, a vagotomy or an antrectomy are eliminated. Neither postgastrectomy syndromes nor marginal ulcers have been encountered among the 14 patients who underwent this procedure, although all of the patients, even those with a pancreatic remnant, evidence marked exocrine insufficiency.[14] The disturbed digestive function occasioned by a proximal pancreatic resection seems to be lessened by preserving the pylorus, but intensive oral enzyme replacement must be started. The 50% six year mortality rate subsequent to pancreaticoduodenectomy reported by Leger et al.[3] was considered secondary to metabolic disturbances. Steatorrhea and malnutrition constituted the cause in one fourth of these deaths. Frey et al.[2] noted that clinically troublesome steatorrhea was more likely to occur after pancreaticoduodenectomy (55%) than after other types of resections. We have been encouraged by the effectiveness of Pancrease®* in relieving refractory steatorrhea in our patients. These capsules of enteric coated microspheres have been shown to be superior to other commercial oral pancreatic enzymes using weight gain and fat utilization in a controlled study.[15]

Retaining a portion of the pancreatic tail at surgery is of course the best protection against the development of diabetes,[2] but when the entire gland must be removed, we inject a suspension containing the patient's own mixed pancreatic cells into the portal vein in an effort to prevent diabetes. This technique involves collagenase digestion and has proven 100% successful in our most recent canine model following total pancreatectomy.[12] Since our first attempt on November 15, 1977, four patients have had transplantation, two of whom had partial success. The inability of the portal system to accept the entire graft suspension owing to a reactive portal hypertension has been a problem. Retrospectively, two of our patients evidenced compromised islet function (decreased insulin response during a preoperative glucose tolerance test) prior to operation as a result of their long-standing pancreatitis. It is hoped that further development of islet cell transplantation techniques will improve the reliability of islet cell reimplantation and minimize the undesirable sequelae of extensive pancreatic resection when required.

References

1. Frey, C. F.: Pancreatic Pseudocyst—Operative Strategy. Ann. Surg., 188:652, 1978.
2. Frey, C. F., Child, G. G., III and Fry, W.: Pancreatectomy for Chronic Pancreatitis. Ann. Surg., 184:403, 1976.
3. Leger, L. and Lenriot, J. P.: Five to Twenty Year Follow-up After Surgery for Chronic Pancreatitis in 148 Patients. Ann. Surg., 184:185, 1974.
4. Mullens, J. E.: Endoscopic Retrograde Cholangiopancreatography (ERCP) in the Diagnosis of Chronic Pancreatitis. Surgery, 84:306, 1978.
5. Nakamura, K., Sarles, H. and Payan, H.: Three-dimensional Reconstruction of the Pancreatic Ducts in Chronic Pancreatitis. Gastroenterology, 62:942, 1972.
6. Prinz, R. A., Kaufman, B. H., Folk, F. A. and Greenlee, H. B.: Pancreaticojejunostomy for Chronic Pancreatitis: Two to 21 Year Follow-Up. Arch. Surg., 113:520, 1978.
7. Sarles, H.: Pancreatitis Symposium de Marseille, 25–26 April, 1962, Basel, S. Karyer Publishers.
8. Sarles, H., Lebreuil, G. and Tasso, F.: A Comparison of Alcoholic Pancreatitis in Rat and Man. Gut, 12:377, 1971.
9. Sarles, H. and Sahel, J.: Pathology of Chronic Calcifying Pancreatitis. Am. J. Gastroenterol., 66:117, 1976.
10. Sato, T., Saitoh, Y., Noto, N. and Matsuno, K.: Appraisal of Operative Treatment for Chronic Pancreatitis—with Special Reference to Side-to-Side Pancreaticojejunostomy. Am. J. Surg., 129:621, 1975.
11. Spiro, H. M.: Some observations on chronic pancreatitis. *In* Beck, I. T. and Sinclair, D. G., (eds.), The Exocrine Pancreas, Baltimore, Williams and Wilkins Co., 1971.
12. Traverso, L. W., Abou-Zamzam, A. M. and Tompkins, R. K.: Effect of an Elemental Diet on Canine Pancreatic Autografts. Surg. Forum, 29:378, 1978.
13. Traverso, L. W. and Longmire, W. P., Jr.: Preservation of the Pylorous During Pancreaticoduodenectomy. Surg. Gynecol. Obstet., 146:959, 1978.
14. Traverso, L. W. and Longmire, W. P., Jr.: Preservation of the Pylorous During Pancreaticoduodenectomy: Follow-up Evaluation in 10 Patients. Submitted for publication.
15. Valerio, D., Whyte, E. H. A., Schlamm, H. A. and Blackburn, G. L.: Enzyme Replacement Therapy in Pancreatic Insufficiency. Parenteral Enteral Nutr., 1:20B, 1977.
16. Way, L. W., Gadacz, T. and Goldman, L.: Surgical Treatment of Chronic Pancreatitis. Am. J. Surg., 127:202, 1974.
17. White, T. T. and Slavotinek, A. H.: Results of Surgical Treatment of Chronic Pancreatitis. Ann. Surg., 189:217, 1979.
18. Wittingen, J. and Frey, C. F.: Islet Concentration in the Head, Body, Tail, and Uncinate Process of the Pancreas. Ann. Surg., 179:412, 1974.

---

* Johnson & Johnson Company. Piscataway, NJ.

DISCUSSION

DR. KENNETH W. WARREN (Boston, Massachusetts): Even though the authors did allude to certain etiologic factors, the success of the operations is proportional to the degree that the operation can correct or circumvent the pathology.

(slide) This graph shows the difference in our clinical material. You will note that a larger number of our patients had had previous operations. The incidence of alcoholism and narcotic addiction were similar. Twenty-eight per cent of our patients had gallstones. Complications including pancreatic cysts, pancreatolithiasis, diabetes, and jaundice occurred in decreasing frequency. Sixteen per cent of our patients had associated peptic ulceration at some time during their illness.

Because of the emphasis that is made with respect to gallstone pancreatitis and alcohol pancreatitis, I point out that 10% of our patients had gallstones and a history of alcoholism. In the patients who had pancreatolithiasis the combination of gallstones and alcoholism was 18%. This further emphasizes the importance of focusing attention on the pathology that is seen rather than on the etiologic factors.

(slide) Some of the items on the slide are merely antecedents; they may be etiologic or they may be associated factors.

It has been pointed out, especially in the manuscript, that when the duct of Wirsung is very large, adequate drainage of the duct by lateral anastomosis will usually give good relief. Some patients may have associated partial or near total obstruction of the distal end of the common duct. In these patients the Roux-en-Y anastomosis to the common bile duct and then to the pancreatic duct as the jejunal limb traverses the neck and body of the pancreas will give a good result.

(slide) This ERCP demonstrates a dramatic phase of pancreatic pathology characterized by marked calcification of the head of the pancreas and an enlarged duct of Wirsung.

(slide) As shown in the drawing, a cyst is situated on the anterior surface of the head of the pancreas and another cyst is present on the posterior surface of the gland. In addition, the duct of Wirsung is enlarged. I elected to do a Roux-en-Y to the anterior cyst and then anastomose this Roux-en-Y limb to the duct of Wirsung. The pancreaticojejunostomy was splinted with a T-tube.

(slide) This is the completion of the operation. The anterior cyst has been anastomosed to the jejunum and the same segment of the jejunum has been anastomosed to the duct of Wirsung.

(slide) This slide shows the cyst which does not communicate with the pancreatic duct. A Pezzer catheter was inserted into the cyst for external drainage. This patient has done extremely well.

I believe that pancreatoduodenectomy and total pancreatectomy have a distinct place in the management of advanced pancreatitis. Over the past 35 years I and my former associates at the Lahey Clinic have performed 186 pancreatoduodenectomies including 31 total pancreatectomies for chronic pancreatitis, with a mortality rate of 3.6%. Only one of 31 patients died after total pancreatectomy. It seems to be a radical procedure, but when you bear in mind that this operation was performed only in patients with far-advanced pancreatitis, it is an appropriate procedure for this phase of the disease.

I agree with the authors that the presence of pancreatic calculi and fibrosis is associated with a large pancreatic duct. These pathologic features facilitate the operation. The results are better not only because of the fibrosis but also because the duct of Wirsung is usually large. Several of the total pancreatectomies were done in stages.

Distal pancreatectomy is a good operation when the disease is confined to the distal part of the gland. However, it is a poor operation when the disease is diffuse.

DR. GEORGE D. ZUIDEMA (Baltimore, Maryland): I would like to direct my remarks toward one portion of this problem; namely, the patient with severe, fixed, chronic pancreatitis requiring massive resections, either a total pancreatectomy or 95% pancreatectomy. These patients on long-term follow-up frequently get into considerable problems with unmanageable diabetes or may wind up chronically disabled in mental hospitals. For this reason in our laboratory we became interested in the possibility of pancreatic islet autotransplantation. Dr. John Cameron and Dr. Dennis Mehigan in our laboratory, and in the clinic now, have concluded preliminary work on animals, and have performed this operation in six patients.

The operation, and the clinical preparation, consists of a 95% pancreatectomy, taking the patient's own gland and mincing it, treating it with collagenase, and then embolizing it within the patient's portal vein. Within the past year, this has been performed on six patients, all of whom have survived, and only one patient now requires insulin.

(slide) I would like to show the clinical course with the plasma glucose levels of one such patient. As you can see, during the first twelve days the patient had elevated plasma glucose levels. These then came down to within normal limits, and only one of these six patients requires insulin on an on-going basis.

Now, by my calculation, Dr. Traverso's group had 16 patients who underwent either total or 95% pancreatectomy, and I was wondering what the long-term results were for this particular group, in terms of diabetes and ease of management.

DR. JOHN S. NAJARIAN (Minneapolis, Minnesota): We have long been interested in islet cell transplantation for diabetics and have done some 21 islet cell transplants into patients with diabetes mellitus. About two years ago we did our first total pancreatectomy, or near-total pancreatectomy, with islet cell autotransplantation into the portal vein. Our results with three patients were presented at the International Congress of the Transplantation Society in Rome last year and was recently published in the proceedings.

As Dr. Zuidema indicated, the pancreas is removed, minced, and digested with collagenase. The islets are then carefully infused into the portal vein, to eventually reside in the liver. None of our patients requires insulin afterwards. Diabetes has been one of the main problems that has been reported with near-total pancreatectomy, and this is a difficult diabetes to control.

In our experience with near-total pancreatectomy, we found that the patient's pain is well relieved. As I noted from Dr. Traverso's slide, there was 100% decrease in pain in the patients who had some form of resection, either a Whipple or a total pancreatectomy, yet he indicated that 45% of the patients were still receiving narcotic drugs. Presumably, the pain was relieved only minimally when compared with a pseudocyst group in which only 26% of the patients were still on narcotic drugs.

I am concerned about this a little bit, because in our experience with near-total pancreatectomy, which, admittedly, is a small series, there was total relief of pain. Although all three patients were addicted to narcotics before, none has needed narcotics since.

My questions may relate to one other facet of that problem. Dr. Traverso, did you note in these patients that were still on narcotics if it was because they were addicted, despite the fact that their pain was gone? Also, what do you think is the role of pain control, that is, injection of the celiac ganglion? We frequently use this procedure, along with others, for chronic pancreatitis, whether a drainage procedure or a near-total resection is being performed. What is the role of celiac ganglion injection?

PROFESSOR MAURICE PAUL MERCADIER (Paris, France): I think it is necessary to discuss the indications for surgical treatment.

In my experience chronic pancreatitis, especially alcoholic pancreatitis, presents in two kinds of patients; 1) Patients without pancreatic insufficiency, exocrine or endocrine, and large duct Wirsung. 2) Diabetic patients with exocrine pancreatic insufficiency and extensive involvement of the gland by sclerosis, calcifications and pseudocysts.

The first type of patient must be treated conservatively. It is not necessary to perform a pancreatectomy. It is sufficient to drain the ductal system by Wirsungojejunostomy with a Roux-en-Y jejunal loop.

(slide) In this patient you can see a calcifying pancreatitis with a stricture of the proximal part of the common duct with dilation of the distal part. The patient had a slight exocrine insufficiency but he was not diabetic. He was cured by a double anastomosis, one at the level of the main pancreatic duct, the other at the level of the hepatic duct. Sometimes a third stricture involves the duodenal loop, most frequently the second part of the duodenum. In such an instance, I add a third anastomosis between the antrum and the jejunal loop as well as a truncal vagotomy to prevent peptic ulceration. The results of such a treatment are good in two-thirds of the patients.

In the second type of patient, when the pancreas is destroyed and the stage of the disease is late with a sclerotic process involving the portal system, the low part of the biliary tree and the duodenal loop, it is mandatory to perform a pancreatectomy: Whipple's operation when the distal part of the gland is normal or an almost total pancreatectomy when there is a band of such tissue along the duodenal loop. We reserve total duodenopancreatectomy for the patient who has total involvement of the gland when the patient is able to observe strict medical treatment to control his diabetic condition.

(slide) This slide shows the results of such treatment in a group of 232 patients. Thirteen patients died in the postoperative period, 219 were followed for at least three years. We have had 67% good results with the conservative procedures: simple, double or triple anastomoses; 82% good results for the Whipple, the same for the distal pancreatectomy or the almost total pancreatectomy. I do not wish to say much about sphincterotomy or splanchnicectomy performed when the disease is operated in its early stage; the results are too poor.

It is necessary to be conservative when pancreatic function is slightly diminished and to be radical when the gland is destroyed and represents the source of complications.

Dr. Ronald K. Tompkins: Dr. Warren, I have to agree with you (and we all do) that the end result of the pancreatitis is what we are dealing with, and the etiology is rather secondary by the time it reaches the surgeon. Furthermore, we appreciate your emphasizing again that the key to the operation is the ductal anatomy.

In the treatment of multiple cysts in the pancreas, which was alluded to also by Professor Mercadier, we probably would tend to resect now more frequently than drain. We have tried the multiple anastomoses and drainages in the past. We think our results now are going to be better with resections. So many of these are in the head of the gland that if we do a Whipple procedure and leave the tail of the pancreas in, this often will mollify, or avoid entirely, postoperative diabetes.

The fact to remember is that in our series, as well as others, the simple drainage of the cyst, as alluded to again by Professor Mercadier, results in at least a third of the patients having recurrent symptoms; so that simple drainage may be the first stage of a multistage treatment.

The questions brought up by Dr. Zuidema regarding the islet cell transplantation are good. We have had experience with four of these procedures since November of 1977, largely due to the efforts of Dr. Traverso. Our success rate is not quite as good as that reported by Dr. Zuidema, in that, of the four, two patients now have what we would call good results; the other two require insulin, similar to a total pancreatectomy.

I should point out, however, that all of our patients had total pancreatectomies, and not 95% pancreatectomy, and I think that may account for some of the difference between his series and ours.

We think that, with perfection of these techniques, as outlined also by Dr. Najarian, the future for resection in the patients with pain caused by chronic pancreatitis is going to be much brighter, and we are thinking now that the future will be more toward resection than to lateral drainage in these patients, because the pain relief is superior with resective therapy. If one can avoid the diabetes, either by injecting the emulsified pancreas back into the patient or by, perhaps, in certain patients, saving the tail of the pancreas, then I think we are going to offer these patients a better result in their chief complaint and the chief indication for operation in these patients, and that is pain.

In answer to Dr. Najarian's question regarding celiac injections, we really haven't had the experience of this being of much value. I know some people have reported that it is of value. In our hands, it has not been, and we tend not to rely on it. We tend to rely on these patients visiting in the pain clinic and making use of all modalities, including psychiatric care, perhaps acupuncture, and other supportive measures postoperatively because there is a difficulty in distinguishing between addiction and actual pain.

This high use of narcotics was something that we were disturbed with in our series, and yet the patients, when questioned, were not having pain. Many of our patients, I'm afraid, were frank abusers of narcotics and did not wish to stop this even after the operation. We need some other help. The knife itself it not going to do the trick.

Professor Mercadier, we thank you again for sharing your experience with us. It is extensive, and in special situations those are remarkably good pearls to take home. We agree with you that sphincterotomy alone is rarely successful, and we prefer not to do that, and I think, as I mentioned, we would do more resections.

Twenty Year Experience in Maxillocraniofacial Surgery

An Evaluation of Early Surgery on Growth, Function and Body Image

JOSEPH E. MURRAY, M.D., JOHN B. MULLIKEN, M.D., LEONARD B. KABAN, D.M.D., M.D., MYRON BELFER, M.D.

We have analyzed 404 patients with a wide variety of maxillary and craniofacial deformities. These do not include head and neck cancer patients as generally defined. Satisfaction has been high as judged by the patients, surgeons and psychiatrists. The complication rate has been significant, approximately 30%, the most common being infection or loss of bone grafts. As experience accumulated, the concept of earlier operative intervention has emerged as an aid in unlocking growth potential, diminishing secondary deformity and improving the development of body image.

FORMERLY MAXILLOCRANIOFACIAL surgery dealt with stable, end-stage deformities in the adult. As experience accumulated results suggested that operations in childhood and even in the neonatal age group would minimize the degree of deformity and lead to better anatomic correction and improved function. This report of 404 patients with congenital and acquired defects supports the concept of performing early surgical correction. The benefits of early operation on growth and function are not surprising; however, the favorable improvement in body image has been unanticipated, gratifying dividend.

Surgery of the face, cranium, orbit, mouth and jaw has evolved into a subspecialty of plastic surgery and draws in addition on the techniques and expertise of neurosurgery, ophthalmology, oral surgery and dentistry. The full team includes otolaryngology, anesthesia, radiology, speech and hearing, nursing, social sciences and a coordinator. The psychiatrist fills an expanding role in the team because the complex patient, physician and family relationship which regulates the psychosocial adjustments changes with growth, development and surgical intervention.

*From the Division of Plastic Surgery,
Harvard Medical School and School of Dental Medicine,
Children's Hospital Medical Center and
Peter Bent Brigham Hospital, Boston, Massachusetts*

Our previous report[11] discussed the preoperative evaluation, anesthesia, surgical technique, results and complications. This report updates our experience with special emphasis on early operation to unlock potential growth, minimize secondary deformity, and enhance the development of body image.

Clinical Material

Four hundred and four patients are evaluated (Table 1). The congenital deformities comprise the largest group. The incidence of trauma requiring craniofacial surgery has increased threefold over the past five years. We are not including conventional head and neck neoplasms in our craniofacial clinic; the tumors seen are usually of mesenchymal origin, located about the cranium, orbits and nasal cavities and occur in a young age group. Of all the patients studied 65% received operations with a total of 385 operations in the 264 patients.

Analysis of the congenital group indicates that the four major categories encompassed by earlier craniofacial surgery, *i.e.*, craniofacial dysostoses, hypertelorism, Treacher Collins and hemifacial microsomia are increasing in number slowly and consistently. However, the inclusion of isolated jaw deformities and secondary cleft lip and palate deformities expanded our series (Table 2).

Surgical Techniques

The techniques have been described previously.[2-4,6,9-18] Recent technical improvements have included advancement of the frontal-orbital complex at the time of the initial operation for craniosynostoses during the first weeks or months of life,[5,7] multiple seg-

---

Presented at the Annual Meeting of the American Surgical Association, April 26-28, 1979, Hot Springs, Virginia.

Reprint requests: Joseph E. Murray, M.D.

Supported in part by the Harry Doehla Foundation, Inc., the Massachusetts Cosmetologists Association, Inc., and the Brigham Surgical Group Foundation, Inc.

0003-4932/79/0900/0320 $01.10 © J. B. Lippincott Company

TABLE 1. *Craniofacial Patients 1959–1979*

	Patients Studied	Patients Operated	Per Cent Operated
Congenital	349	224	64
Acquired	55	40	71
tumor	28		
trauma	27		
Total	404	264*	65

* Three hundred and eighty-five operations in 264 patients.

mental osteotomies for unilateral orbital deformity and varieties of maxillary and mandibular advancements and setbacks with and without segmental osteotomies. The operations fall into four general categories in degree of magnitude (Table 3). The most extensive operations are those involving craniotomy with exposure of the brain and those with facio-orbital osteotomies and interposition bone grafts. These long procedures may require combined neurosurgical participation during portions of the procedure. These operations usually are for correction of hypertelorism, and midface stenosis seen in Crouzon's or Apert's syndromes; or for intracranial approach to tumor resection and trauma cases. The next most extensive operations are those requiring facio-orbital dissections, osseous contouring, and onlay bone grafting: examples are correction of Treacher Collins deformity. Without an osteotomy, morbidity in these procedures is less, but the full dissection of both orbital contents constitutes a very real hazard. Next in magnitude are the operations of the maxilla and /or mandible requiring osteotomy with or without bone grafts. Although the duration of anesthesia and operation may be shorter in this category than in the previous two, critical complications can occur. Whenever jaw osteotomies, either segmental or complete are performed, an increased hazard is introduced by the need for intermaxillary fixation requirements with airway hazards constituting a major source of complication. The least extensive operations are those with soft tissue dissections and repairs such as, secondary repair of oronasal communications or nerve deficit.

TABLE 2. *Congenital Deformities 1959–1979*

Craniofacial dysostosis		61
Craniosynostosis	12	
Crouzon's	26	
Apert's	19	
Other	4	
Hypertelorism		23
Treacher Collins		14
Hemifacial Microsomia		38
Other		213
congenital tumors (vascular, neurofibroma, encephalocele)	14	
isolated jaw deformities (prognathism, maxillary deformity, chin)	108	
late cleft lip & palate deformities	31	
facial clefts	5	
facial atrophy	12	
miscellaneous	43	
Total		349

TABLE 3. *Magnitude of Operation*

+ + + +	Craniotomy, facio-orbital osteotomy, interposition bone graft
+ + +	Facio-orbital dissection, osseous contouring, onlay bone graft
+ +	Maxillary and/or mandibular osteotomy with or without bone graft
+	Soft tissue dissection and repair

Psychiatric Testing

In semistructured interviews the psychiatrist focuses on the stages in body image development. These interviews are supplemented by the Draw-A-Person exercise, the Piers-Harris evaluation with both mother and child, and the Sears test. These provide objective assessments of self concept.

Results

The aim of the treatment is to allow the patient to enter the "mainstream" of life. Correction of anatomy and function are merely means to that end. In this light we have considered our operative results from three viewpoints: patient, surgeon, and psychiatrist (Table 4). As in other areas of plastic surgery, patient satisfaction is higher than the surgeon's anatomic assessment. It was a surprise, however, to find the psychiatric evaluation surpassing the surgeon's impression of the degree of patient contentment. Several patients with incomplete anatomic reconstruction achieved almost complete social integration and significant personality improvement.

Complications

The overall incidence of complications was 30% (Table 5). The most severe complication was an un-

TABLE 4. *Assessment of Operative Results*

	Per Cent Good	Per Cent Average	Per Cent Poor	Number of Patients
Patient and psychiatrist	88	8	4	60*
Patient and surgeon	80	13	6	200†
Surgeon's anatomic assessment	70	22	8	208†

* Interview of 60 consecutive patients following operations of + + + and + + + + magnitude.
† Postoperative clinic notes by surgeons.

TABLE 5. *Complications in 264 Operated Patients*

Death	1*
Blindness	
unilateral complete	1
unilateral partial	1
Hemorrhage	
greater than ½ BV	7
operation stopped	3
Airway—prolonged intubation or tracheostomy	6
Infection—I&D or antibiotics	20
Bone graft loss	
minor	7
major	14
Central nervous system	6
Other	
hematoma, wound dehiscence	6
trismus	4
donor site	4
flap loss	1
Total	81 (30%)

* Unexplained respiratory arrest 36 hours postextubation.

explained respiratory arrest 36 hours following endotracheal extubation in a patient who had had a Grade + + operation, *i.e.*, a segmental osteotomy and genioplasty. She had had an incidental dilatation and curettage for a gynecological condition utilizing the same anesthesia. Unilateral blindness occurred in two patients. In both instances orbital swelling was noted in the final stage of the operation and immediate decompression was performed with the ophthalmologist in attendance. In one patient, improvement seemed to occur for 36 hours only to be followed by relapse at 48 hours. In the other patient the unilateral orbital swelling was decompressed immediately but vision never returned.

Airway problems occurred in operations which required intermaxillary fixation. Bone graft loss of major degree was noted in 14 patients. There were six central nervous system complications with leakage of cerebrospinal fluid; all corrected by secondary surgical repair.

Current Concepts of Treatment

Early operative correction, performed as safety allows, is based on three guiding concepts: unlocking potential growth, minimizing secondary deformities, and aiding the development of body image.

Unlocking of Growth Potential

Excision of prematurely closed cranial sutures improves the skull shape and allows the brain to grow. Failure to correct the synostosis of the frontoethmoid, frontosphenoid and the sphenozygomatic suture lines results in a furrowed forehead deformity and may contribute to underdevelopment of the midthird of the face. Conventional coronal craniectomies allow adequate development of the cranial vault; however, there may be restriction of growth in the frontal area and secondary distortion of the occipital bones (Fig. 1a). The forehead

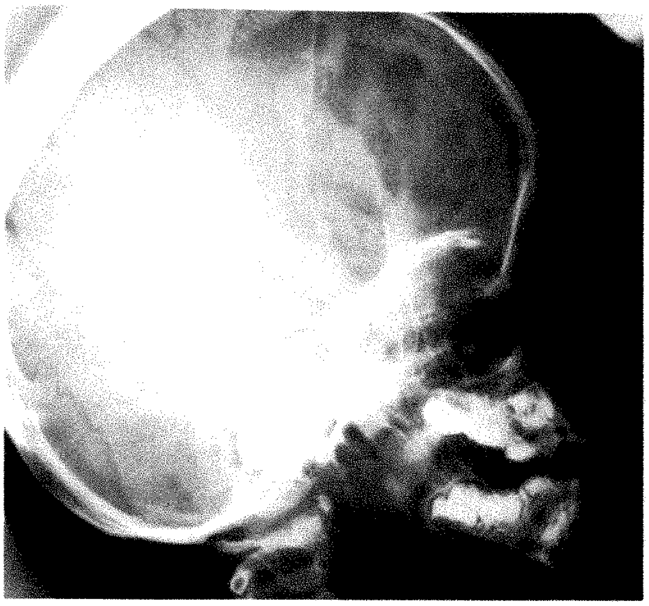


FIG. 1a. Postoperative x-ray of skull in a year-old patient who had coronal strip craniectomies in infancy. Note flatness of forehead and supraorbital regions, with secondary distortion of occipital region.

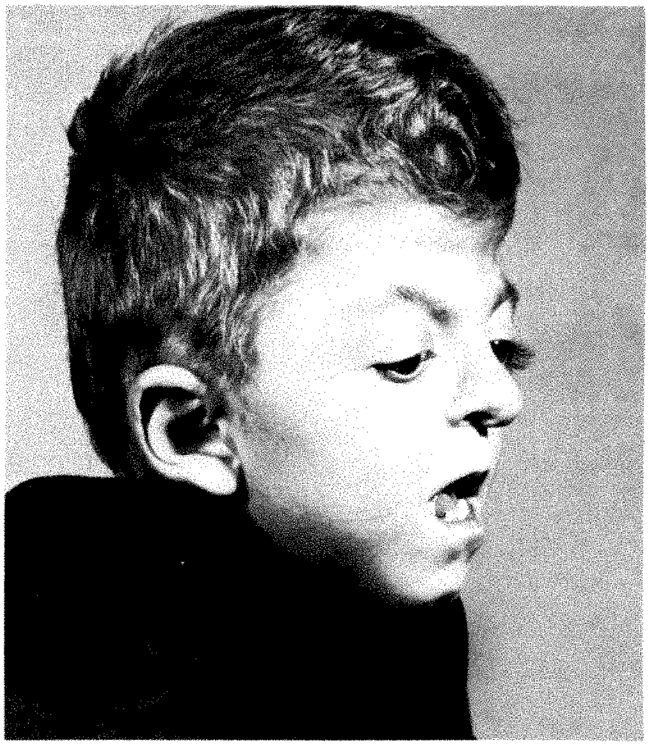


FIG. 1b. Early craniectomy failed to prevent typical grooved forehead in this 8-year-old with Apert's type craniosynostosis.

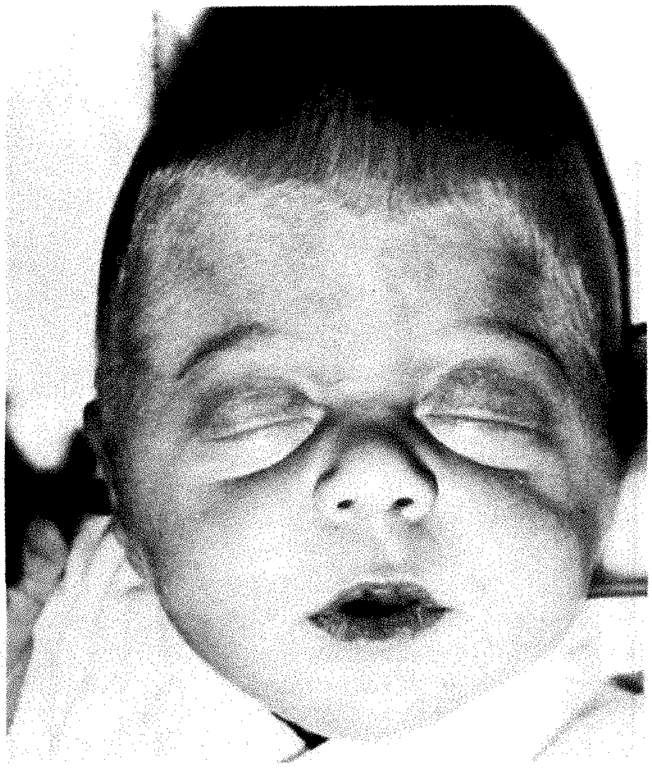


FIG. 2a. Preoperative view of a 6-week-old infant shows oblique concavities in frontotemporal areas, a result of synostosis of the frontoethmoid, frontosphenoid, and frontozygomatic sutures.

deformity with grooving of the brows bilaterally in a patient with coronal synostosis who had conventional coronal craniectomy is shown in Figure 1b. In contrast, the concave, oblique forehead grooves in an infant prior to early intervention (Fig. 2a) have been corrected by extended craniectomy including release of the appropriate frontal orbital sphenoid and zygomatic sutures in addition to standard coronal craniectomy (Fig. 2b). The forehead advancement is maintained in a more normal position by the developing brain. This additional osteotomy adds less than 30 minutes to the operative time because the bones are soft and malleable and can be osteotomized more easily than in the older child or adult. The postoperative result is far superior to that which could be obtained by secondary operations at a later date. The contrast between the results of early and late correction can be seen by comparing Figures 1b and 2b.

Failure to unlock growth in a unilateral coronal synostosis may produce an increasing deformity as adjacent areas with normal open suture lines passively expand. The constriction of growth in one area of the cranium thus acts as a tether or lock and the normal tissues develop around it in a distorted way. Bossing of the normal area and displacement of adjacent structures may result (Figs. 3a and b). Correction at a late stage is vastly more complex than surgery performed in the first few months of life. The late operation often requires craniotomy and transposition of frontoparietal bone segments along with osteotomies of the orbits and frontonasal complex. Bone grafts are required to stabilize the osteotomized segments and to improve contour (Fig. 3c). Unlocking growth potential on the affected side allows normal growth stimulation in adjacent areas by the expanding brain acting as a "functional matrix."[8] In summary, early operation is easier, shorter, and more effective.

Minimizing Secondary Distortion

Secondary deformity may be produced in ways other than by overgrowth compensating for a restricted site. Any mass can distort adjacent growth. This is seen in congenital tumors such as vascular malformations, neurofibromas or encephaloceles. Secondary and even tertiary effects are produced with a frontoethmoidal encephalocele (Figs. 4a and b). As the encephalocele extrudes through the frontonasal defect, distortion of adjacent tissues can be produced. The eyebrows are displaced upward and laterally and orbital hypertelorism is present. This congenital mass acted as a wedge in

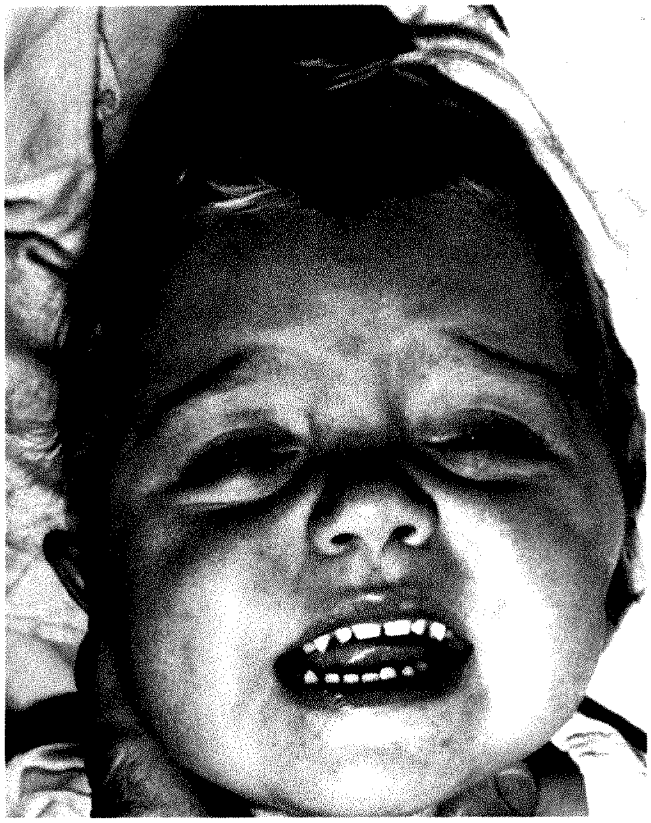


FIG. 2b. One year later the correction of the forehead and brow by extended craniectomies is seen. This correction will be maintained by normal brain growth.

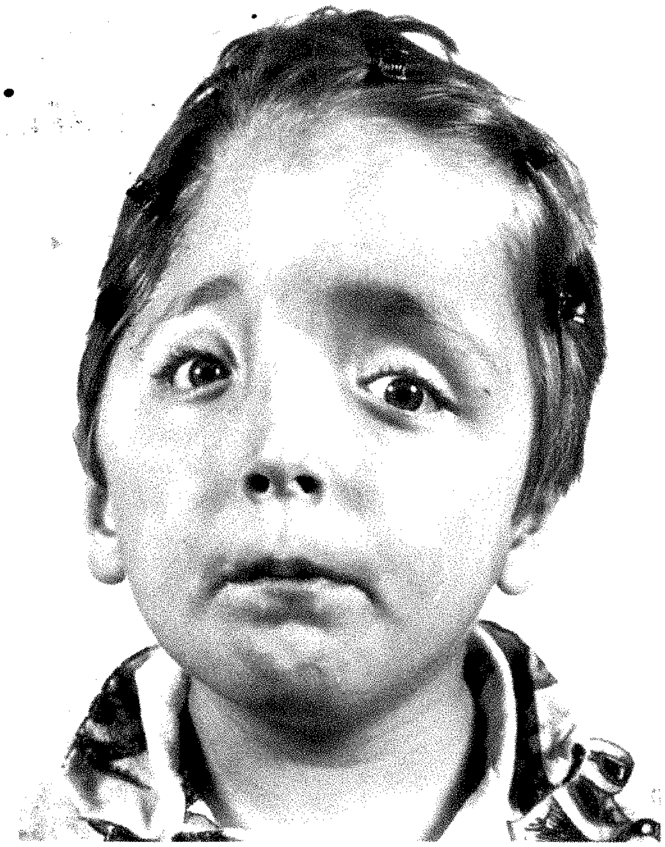


FIG. 3a. Severe distortion of forehead, orbits and nose results from uncorrected unilateral synostoses.

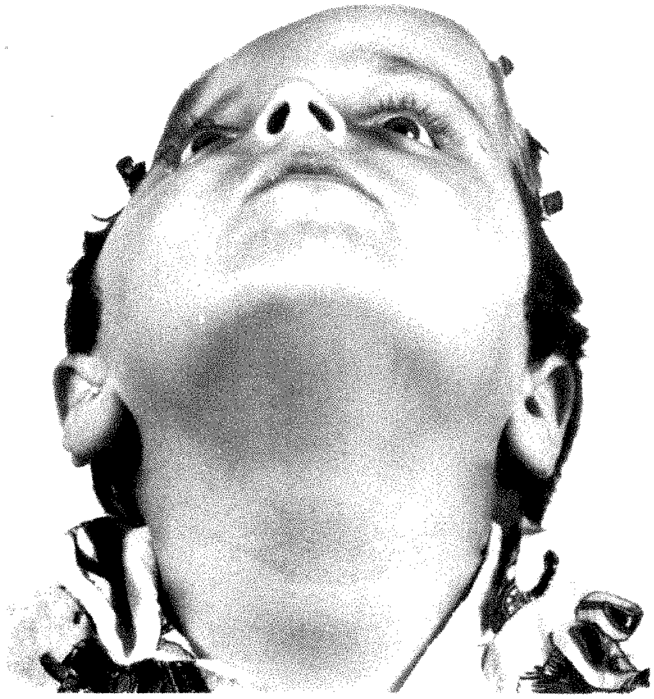


FIG. 3b. The tethering effect centered in the right brow and forehead areas is accentuated by overgrowth of unrestricted left forehead. Note obliquity of nose and midface.

the middle of the face, and gradually caused elongation and lowering of the maxilla and mandible. It appears as if a horizontal disjunction had occurred at the level of the equators of the orbits. X-rays (Figs. 4c and 4d) show the distortion of the orbits with the orbital processes of the frontal bone displaced superiorly, the nasal bones displaced inferiorly, and a large open conduit between the two into which the glial contents have herniated. At operation it was noted that the brain had assumed the shape of the defect. Correction consisted of resection of the protruding encephalocele and repair of the dura defect with reinforcement by a bone graft. Bone grafts were also used to reconstruct the nose, the roofs and medial walls of the orbit. Soft tissue resection completed the correction (Figs. 4e and 4f). Good restoration of the contour of the forehead was obtained along with repositioning the eyebrows. There is still minimal flatness of the bridge of the nose and the major secondary defect, elongation of the face, was not completely correctable. This will be extremely difficult to correct if the patient ever does desire it for it would require an intrusive, horizontal osteotomy at the level of the infraorbital vessels.

The concept of minimizing secondary deformity applies most critically at early age when growth potential is maximal and deformity is minimal.

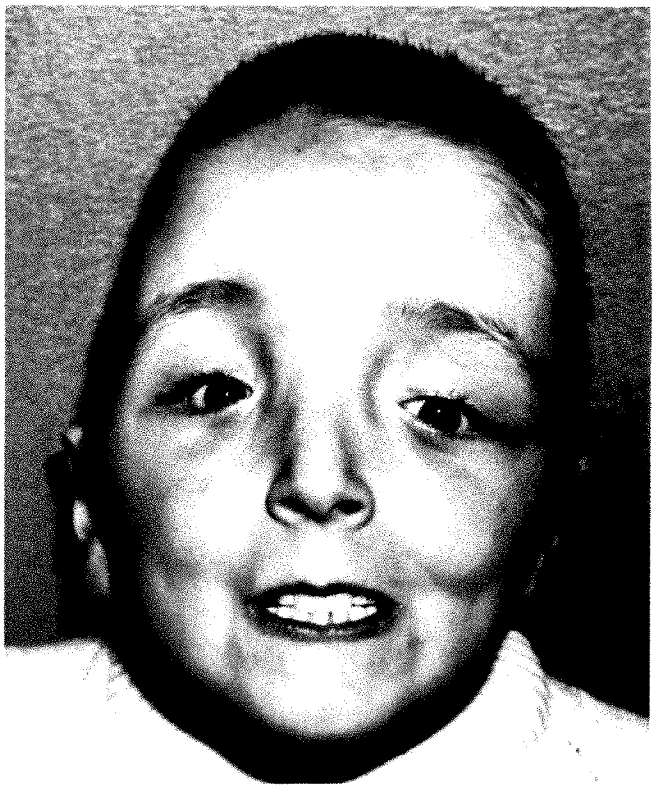


FIG. 3c. Correction of forehead, orbit and nose required intracranial and facial exposure, with transposition of calvarial segments, interposition and onlay bone grafts, plus orbito-fronto-nasal osteotomies. This complex operation could have been avoided by earlier surgical correction.

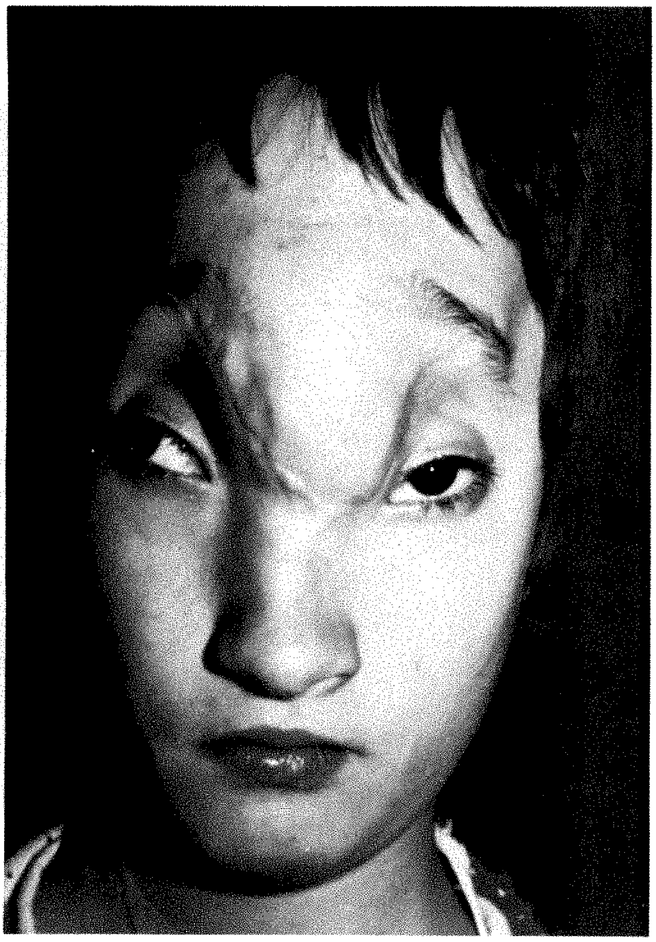


FIG. 4a. Late result of uncorrected frontoethmoidal encephalocele reveals secondary elevation of brows, lateral displacement of orbits, and vertical elongation of the central 1/3 of the face.

Aiding the Development of Body Image

Body image is a psychological concept and not merely a function of objective appearance. Often changes in body image are confused with physical change following surgical intervention. Change in body image, however, involves a complicated process occurring over time and is a result of psychological development of the child, the surgical procedures, and the societal and familial factors. Craniofacial operations produce rapid and dramatic change in objective appearance and thus allow opportunity to study the evolution of body image over a compressed time span.

Body image development can be viewed in four stages; cognitive growth, perception of body stimuli, the stimuli from the environment in the form of comparison and the response of others. Because the child starts to define his body image far earlier than school age, earlier surgical correction is more likely to allow its normal development. Surgical intervention may produce objective physical change without a corresponding rapid change in body image. The modification of an established body image can also be analyzed in four components: the decision to undergo operation; the operative experience; the immediate postoperative period and the reintegration stage.

The deformity which most strikingly exemplifies the development and changes in body image is hemifacial microsomia, the first and second branchial arch syndrome. Always asymmetric, the deformity may be minimal at first but as growth of the normal side occurs the defect becomes more obvious. The deformity has a variety of physical manifestations focused either on the external ear or mandible, or both. Secondary involvement of the zygoma, orbita, maxilla and cranial nerves occurs frequently. If uncorrected the deformity will progress in the adult stage to a constriction of the entire facial skeleton with gross distortion of the occlusal plane and shortening of the vertical height of the face.

Until recently surgical correction was focused on the external ear deformity. Currently with the application of craniofacial techniques correction of the bony deformity has become possible. Now the skeletal deformity takes first priority in repair with external ear reconstruction and soft tissue repairs performed later. Correction of the adult deformity requires a complex

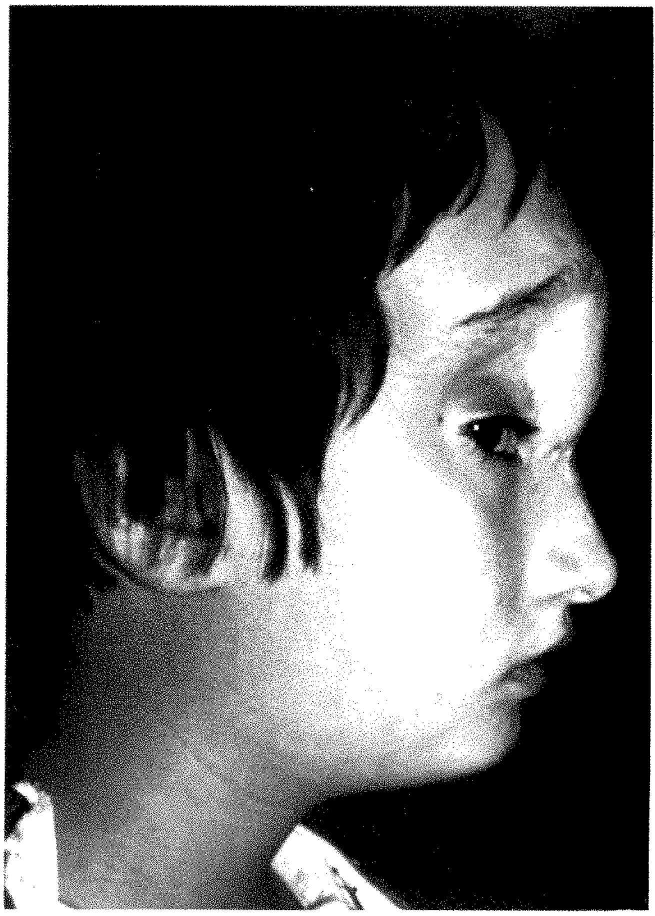


FIG. 4b. Lateral view shows herniated encephalocele and striking expansion in nasofrontal region.

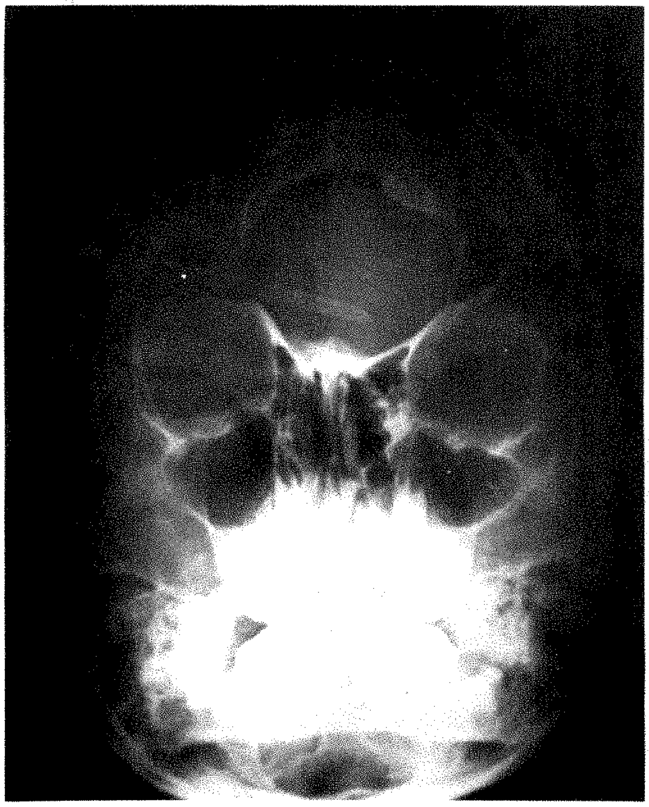


FIG. 4c. A-P x-ray reveals large defect in forehead and lateral displacement of medial walls of orbits.

operation involving osteotomies of the mandible and maxilla, often combined with genioplasty, onlay bone graft to the zygoma and occasional orbital osteotomies.[12] The complexity of the repair in the adult is in itself a stimulus to seek more effective, earlier intervention.

There has always been reluctance to operate on growing patients for fear of disturbing growth. However, these deformities become worse spontaneously with continued growth of the normal side so earlier intervention does not produce a more severe end result.

A striking change in body image occurred in an 11-year-old patient with hemifacial microsomia operated upon for the first time (Figs. 5a and b). As part of his regular preoperative psychiatric interview and work-up he was asked to draw the picture of "a man," not a sketch of himself, but merely his perception of an individual man. His operation was major involving bilateral mandibular osteotomies with elongation of both rami, creation of a temporomandibular joint, rotation genioplasty, and correction of an open bite. As part of regular postoperative psychiatric testing the "Draw-A-Person" test was repeated. His preoperative drawing showed an asymmetrical, amorphous, fluid figure, with uneven face, mouth, shoulders and extremities (Fig. 5c). The postoperative drawing was box-like, symmetrical, a squared figure (Fig. 5d). This seems to be objective evidence of an alteration in his response to sensory stimuli, both from himself and others. Parenthetically, his anatomic improvement, although significant, was not dramatic and was by no means commensurate with his marked improvement on his self-image. This patient is a good example of patient's satisfaction exceeding that of the surgeon's. It also illustrates the critical nature of the psychiatric evaluation.

Discussion

Surgical decision making is always evolving. The variety of deformities and the intricacies of adaptive responses and the improvement in surgical techniques have changed some of our fundamental premises. Formerly reconstructive surgeons were content to restore anatomy and bodily function expecting to im-

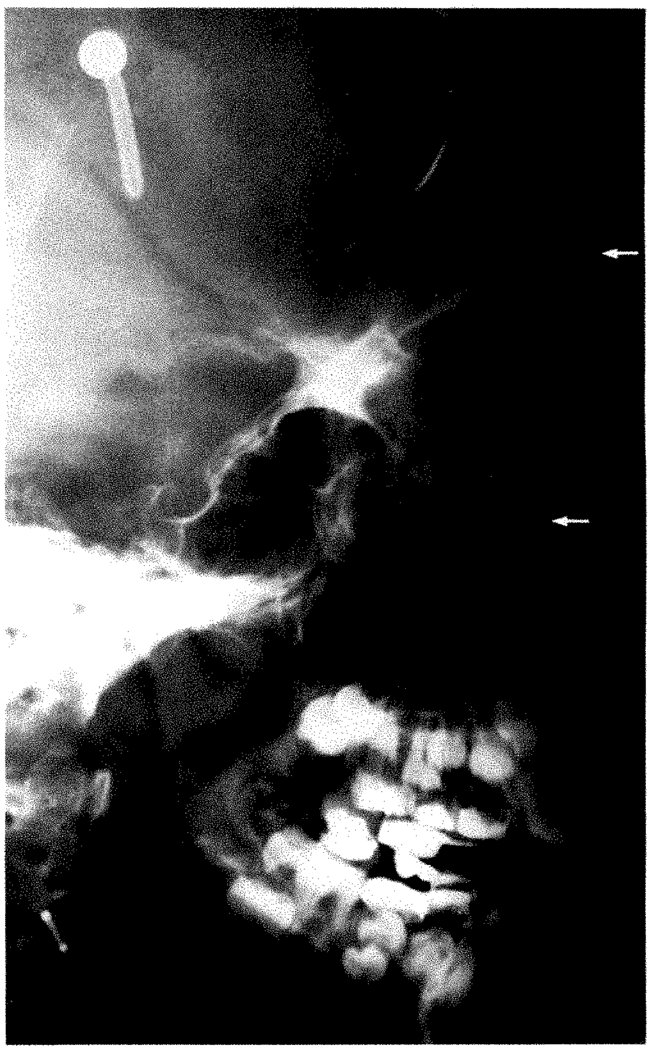


FIG. 4d. Lateral x-ray shows frontal bone displaced upward (upper arrow) and nasal bones downward (lower arrow) revealing wide communication through which the encephalocele herniates.

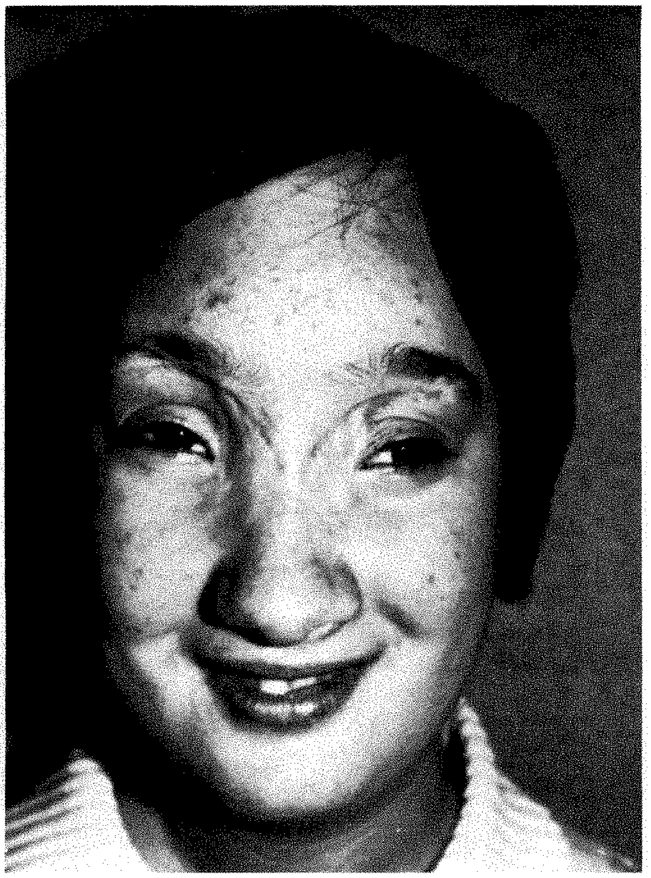


FIG. 4e. After resection of encephalocele and repair of dural defect with fascia. Forehead, orbits and nose were repaired with bone grafts. Note correction of brows and medial canthi.

prove automatically the psychological adjustment of the patient. Patient satisfaction is our primary aim. Often a patient with minimal correction displays a disproportionate satisfaction. Conversely, striking surgical correction of the deformity may not lead to patient satisfaction but instead may precipitate more critical introspective analysis of the residual defects. This occurs more often following treatment for cancer or trauma, for these born-normal patients compare themselves to their original state rather than to their immediate preoperative condition.

Realization of the benefits of early operation has evolved slowly. Previously we were hesitant for fear of disturbing "growth centers." Retrospective and prospective studies indicate that growth disturbances are not accentuated by operation. Therefore early intervention, with unlocking growth potential and prevention of secondary deformation, is supported by our experience. Optimal function influences growth favorably.[8] In addition, early operation improves the development of body image.

The body image concept occupies an important role in indications for surgery; therefore, analysis of the stages of its evolution is warranted. The first step, the child's *cognitive development*, influences a child's perception of his body and defines the limit of his body image. This analysis is complicated because patients who look dull and retarded frequently are considered so regardless of their true intellectual ability. Many patients with normal intelligence have been rescued from custodial institutions and restored to the "mainstream" following surgical correction. Society tends to underestimate the intellectual ability of physically disfigured people and intellectual assessment has not always been carried out appropriately.

A second stage influencing body image development is the *perception of stimuli* by the patient himself. These perceptions can be influenced by the congenital anomaly. Congenital orofacial and upper extremity anomalies result in relative sensory deprivation. Children denied the sense of oral gratification and stimulation from grasp develop a sense of bodily incompetence in association with their functional impairment.

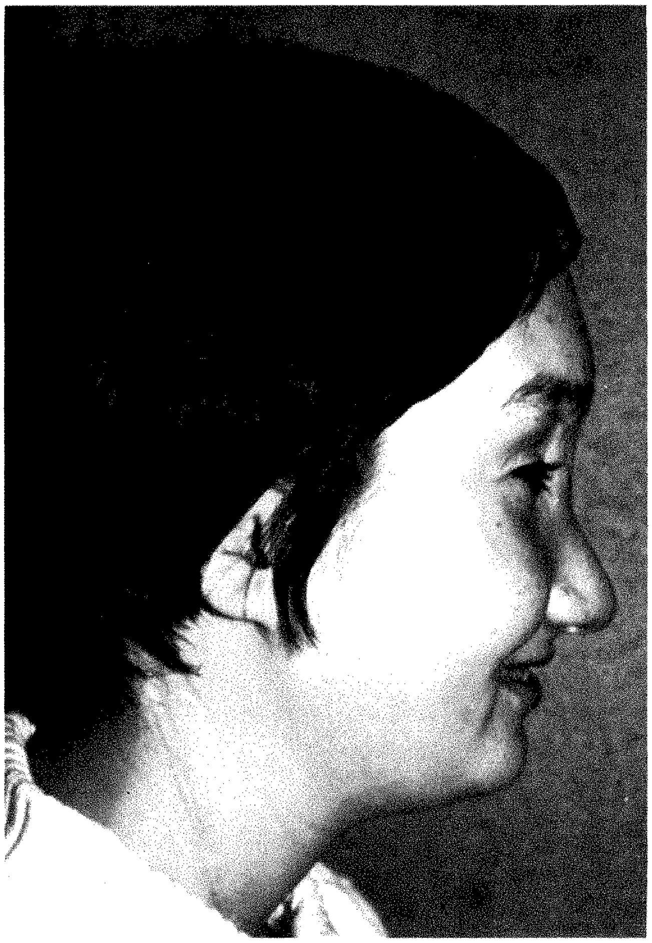


FIG. 4f. Lateral view reveals excellent correction of forehead and brow, but elongation of nasofrontal angle still persists.

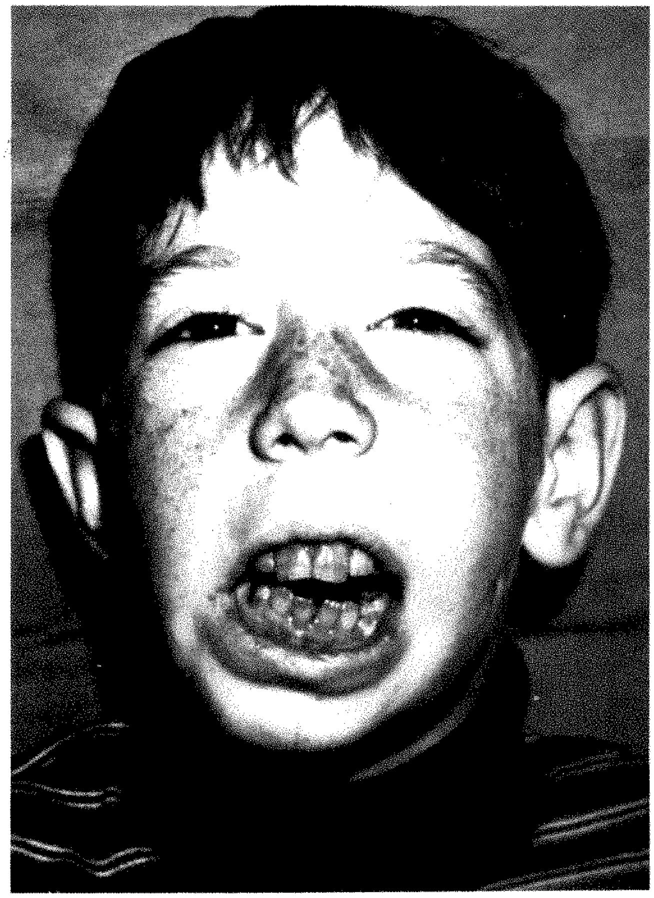


FIG. 5a. AP view of 11 year old with bilateral asymmetrical hemifacial microsomia reveals open bite, deviation of chin to right, oblique occlusal plane, and soft tissue deficiency of right side of face.

The third element in body image formation is *stimulation from the environment* in the form of comparisons to others. The child compares his body with those of his parents and peers noting similarities and differences. This sense of differentness increases as the patient gets older and usually is not verbalized.

The fourth element in body image development is the *response of others*. Parents are often disappointed in not having the idealized child. The responses from society tend to isolate the youngster or present him with a negative view of his deformity. Parents and youngsters often react by identifying the deformity as something "cute" or "special" or may equate deformities with a sense of "badness" in relation to other family members.

Children with lesser intelligence focus more on functional limitations as a defense mechanism and deny any cosmetic significance to their deformity. These youngsters become more appreciative postoperatively, because they are freed of their defenses. Any deformity, congenital or acquired, may inhibit normal psychological growth. The fact that inhibition develops following acquired deformities supports the concept that impairment may be minimized by early operative intervention.

The change in body image following operation demonstrates its adaptability and this occurs in four components. First, there is a complex decision to undergo surgery. The timing of this decision is based on social awareness, self-recognition, parental and peer pressure, emotional state, and the surgeon's assessment. The second phase, the operative experience, provides concrete evidence that a change in physical appearance has taken place. The reality of intervention is now acknowledged. Prior to intervention there is always the opportunity to indulge in fantasies. The third phase, the immediate postoperative period, involves physical pain, increased rather than decreased distortion of physical appearance and re-examination of the decision and expectations. This postoperative phase is a psychological crisis with an opportunity to lay better groundwork for subsequent integration. Disruption of the previous psychological defense often leads to

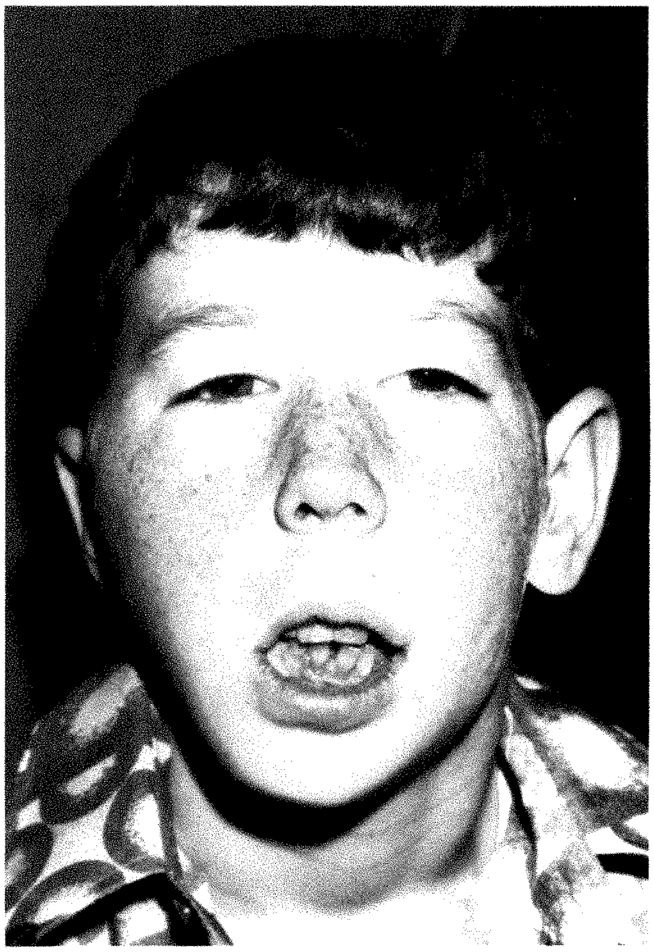


FIG. 5b. This is a postoperative view following bilateral mandibular osteotomies with elongation of both rami, construction of a temporomandibular joint, rotation genioplasty and correction of open bite. Occlusal plane is level.

introspection with acknowledgement of the previously existing deformity. During the fourth or reintegration phase, the psychological defenses reorganize: with increased intellectual freedom, a changing of social priorities, and increased interpersonal relationships. This phase may last from six weeks to six months postoperatively.

Change in body image does not necessarily correlate with the degree of anatomic improvement. In addition, intellectual function is often improved despite the absence of any organic change. Consequently children perform better at home; and in school some children can be transferred from the specialized programs to the regular classroom. Following trauma or tumor the patient often denies the deformity until the operative correction has been performed. Depression, withdrawal, and eventual alteration in behaviour may be seen in the patient with posttraumatic deformity.

This type of patient is especially vulnerable during the late postoperative period.

Our craniofacial team's overview of child development is illustrated in Figure 6. The normal milestones occur at infancy, school age, adolescence, and adulthood.

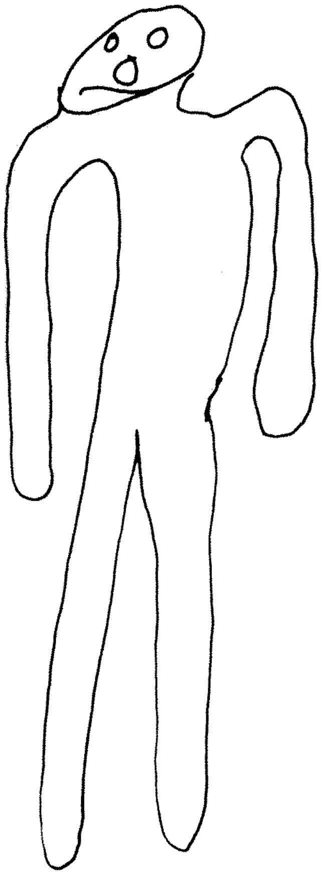


FIG. 5c. This sketch was produced preoperatively by the paient in Figure 5a when tested by standard "Draw-a-Person" test in which he is asked to draw a picture of "a man."

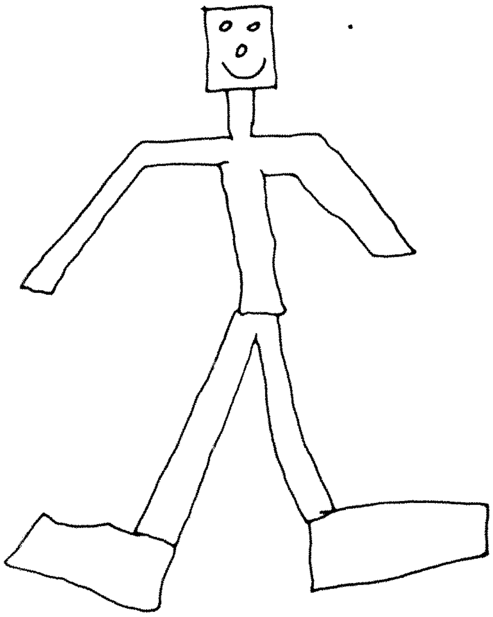


FIG. 5d. Same test when repeated 6 weeks postoperatively, reveals striking change in body image.

At each level psychological function exerts its influence in specific ways. For example, a deformed infant, when deprived may drift further and further from the "mainstream" as a sense of loss and disruption of parental bonding exerts its influence. The parents, expecting the idealized child, have a difficult adjustment to make at birth. During infancy, there is a normal pattern of increasing sense of competence with sensory input from hands, mouth, eyes, ears, and nose. Congenital deformity may lead to a sense of incompetence, isolation, and eventual psychological constriction.

At school age peer interaction, cognitive growth and mastery of skills assume increasing importance. Now the deformed child is again handicapped and thwarted. Peer isolation begins, lowered cognitive performance and a failed sense of mastery becomes a subconscious part of his very being.

During adolescence when consolidation of identity, heterosexuality, career goals and resolution of conflict are major problems, even in the most physically endowed, the deformed youngster becomes further and further separated from his peers. There is uncertain sense of identity, diminished career goals, a feeling of seclusion and failure which often envelopes the patient.

Whereas the normal adult has a family, career satisfaction, peer acceptance and a sense of completeness, the deformed adult has a sense of isolation, diminished achievement, incomplete feeling, conflict and hostility.

Surgical intervention at any phase tends to shift the deformed patient toward normal pathways. In contrast a defect from trauma or tumor occurring in a normal person tends to shift development away from the

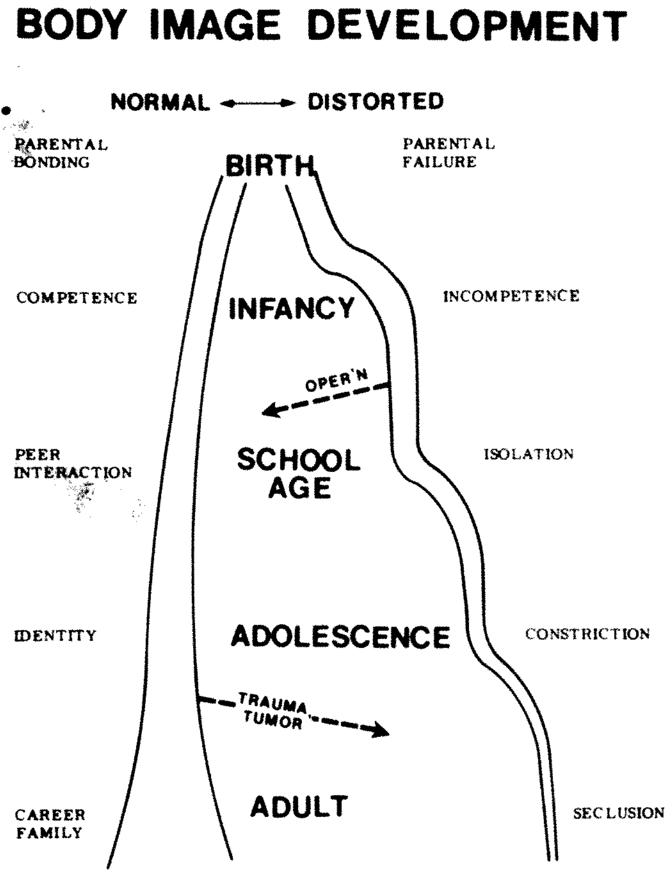


FIG. 6. The contrasting pathways of development between normal and distorted diverge more with each milestone of infancy, school age, adolescence, and adulthood. Note progressive constriction leading to isolation and seclusion in the deformed person.

"mainstream." Our thesis is that earliest possible correction of deformity makes the journey easier, shorter and more complete.

Acknowledgments

We would like to acknowledge the Departments of Neurosurgery, Radiology, Ophthalmology, Otolaryngology, Dentistry, Anesthesia and Social Services.

References

1. Belfer, M. D., Harrison, A. M. and Murray, J. E.: Body Image and the Process of Reconstructive Surgery. Am. J. Dis. Child., (in press).
2. Converse, J. M., Ransohoff, J., Mathews, E. S., et al.: Ocular Hypertelorism and Pseudohypertelorism. Plast. Reconstr. Surg., 45:1, 1970.
3. Converse, J. M., Wood-Smith, D. and McCarthy, J. G.: Report on a Series of 50 Craniofacial Operations. Plast. Reconstr. Surg., 55:283, 1975.
4. Edgerton, M. T., Jane, J. A., Berry, F. A. and Marshall, K. A.: New Surgical Concepts Resulting fraom Cranio-orbito-facial Surgery. Ann. Surg., 182:228, 1975.
5. Hanson, J. W., Sayers, M. P., Knopp, L. M., et al.: Subtotal Neonatal Calvariectomy for Severe Craniosynostosis. J. Pediatr., 91:257, 1977.
6. Marchac, D.: Radical Forehead Remodeling for Craniostenosis. Plast. Reconstr. Surg., 61:823, 1978.
7. McCarthy, J. G., Coccaro, P. J., Epstein, F. and Converse, J. M.: Early Skeletal Release in the Infant with Craniofacial Dysostosis. Plast. Reconstr. Surg., 62:335, 1978.
8. Moss, M. L.: Twenty Years of Functional Cranial Analysis. Am. J. Orthod. 61:479, 1972.
9. Munro, I. R.: Orbito-cranio-facial Surgery: The Team Approach. Plast. Reconstr. Surg., 55:170, 1975.
10. Murray, J. E. and Swanson, L. T.: Mid-face Osteotomy and Advancement for Craniosynostosis. Plast. Reconstr. Surg., 41:299, 1968.
11. Murray, J. E., Swanson, L. T., Strand, R. D. and Hricko, G. M.: Evaluation of Craniofacial Surgery in the Treatment of Facial Deformities. Ann. Surg., 182:240, 1975.
12. Murray, J. E., Kaban, L. B. and Mulliken, J. B.: Craniofacial Abnormalities. *In* Ravitch, M. M., Welch, K. J., *et al.* (eds.) Pediatric Surgery, Chicago, Yearbook Medical Publishers, Inc., 1979, pp. 233–248.
13. Ortiz-Monasterio, F., Del Campo, F. and Carrillo, A.: Advancement of the Orbits and the Midface in One Piece, Combined with Frontal Repositioning, for Correction of Crouzon's Deformities. Plast. Reconstr. Surg., 61:507, 1978.
14. Tessier, P.: Ostéotomies totales de la face; syndrome de Crouzon; syndrome d'Apert; oxycéphalies, scaphocéphalies, turricéphalies. Ann. Chir. Plast. 12:273, 1967.
15. Tessier, P.: Relationship of Craniostenoses to Craniofacial Dysostoses and to Faciostenoses. Plast. Reconstr. Surg., 48:224, 1971.
16. Tessier, P.: The Definitive Plastic Surgical Treatment of the Severe Facial Deformities of Craniofacial Dysostosis. Plast. Reconstr. Surg., 48:419, 1971.
17. Tessier, P.: Experiences in the Treatment of Orbital Hypertelorism. Plast. Reconstr. Surg., 53:1, 1974.
18. Whitaker, L. A., Schut, L. and Randall, P.: Craniofacial Surgery: Present and Future. Ann. Surg., 184:558, 1976.

DISCUSSION

DR. BRADFORD CANNON (Boston, Massachusetts): During World War II, he contributed to the rehabilitation of wounded personnel with severe injuries to the extremities and hands. His next interest was focused on the problems of the failing kidney, to the solution of which problems he has made most significant contributions, both in the techniques of kidney transplantation, and also in the discovery, control and use of the immunosuppressive agents used in prolonging the survival of such kidneys.

Dr. Murray is one of a handful of world leaders in maxillocraniofacial surgery. As Dr. Murray has told us, the significance of these procedures to the growing child speaks for itself.

For myself, I enjoy papers such as this, in which I cannot only see, but almost touch and feel the procedure and the result. Dr. Murray's paper struck me as one to be enjoyed because the results can be visualized.

Dr. Murray, your follow-up study is a most enlightening report, and an inspiration to all of us, aware as we must be that every individual is concerned about his or her appearance. You have shown us ways in which some of the most seriously deformed can be helped.

DR. MILTON T. EDGERTON (Charlottesville, Virginia): At Charlottesville, we have some modest differences in technical approaches to the patient with craniofacial deformities, but we would agree "right down the line" with the major points of Dr. Murray's thesis today.

I realize that most of you are not dealing daily with these patients, but I suspect all of you are interested from time to time in catching up with the state of the art in any specialty that affects the total welfare of a child.

I like to think that early surgical treatment of these children will give us most of the practical answers to the problems we are facing, but it is more complicated than that. I would like to show one child who illustrates some of the considerations that Dr. Murray referred to.

(slide) This baby was operated on at two weeks of age, and the case raised some interesting points, at least to our group. This 2-week-old baby had a cranio-orbitofacial deformity, which, as you heard earlier, would increase with time, if untreated. We were concerned also because of the danger of amblyopia in the occluded left eye.

(slide) The asymmetry seen on the x-ray reflects something that was useful in the treatment of this child, namely, that the asymmetry of the problem gave us an opportunity to modify only the affected side, and thus learn something about the resulting growth problems and about the secondary deformities, such as downward displacement of the left eye and the left maxilla.

You heard from Dr. Murray that reshaping of the abnormal cranial bones may allow the brain to assume a more normal shape and guide the morphology of regenerating bone. We know this, will happen in most instances. In some instances, the dura also is a restraining element, and we have found occasions on which the dura needed to be released and grafted, or plicated, at the time of craniectomy in order to reshape the brain.

This was done for this child (slide), and the dural graft is shown being placed in the flattened right frontal region to make room for the brain. (slide) The left eye was lifted as much as possible, but no maxillary osteotomy was done on this two-week-old baby. A K-wire was used to support the orbital bone.

(slide) The result was quite encouraging. We had an excellent shaping of the head, a good-looking eye on the left side, almost completely corrected as to level. We were convinced that early operation provided the best answer.

(slide) Notice something interesting that developed in this child two years later. The right frontal region, precisely in the area of the dural release, showed an actual overcorrection, and a formerly flat area was bulging. This was informative as to the role of the dura, but it was not satisfactory in regard to the child. The left eye, you notice, was still slightly low as compared with the right eye.

(slide) At a second procedure, we elected to go about what we had planned from the first, that is, an orbital-maxillary osteotomy to raise the left eye. You can see the orbit being shifted upward by removal of frontal bone above the left eye (slide). Then we went back and tried to redo (slide) (and this is simply a detail of the surgery) what we had overdone with the dura in the right frontal region, namely, to plicate it to see if we could control the overgrowth and bulging at the site of the original dural graft. Some bone islands of cranial bone were simply placed back over the now plicated dura (slides). These views show the resultant positioning of the orbit.

(slide) Because the globe will not come up by itself when you raise the orbital bone roof, an implant is placed under the globe, to lift and support the soft tissue of the globe. We thought we were doing pretty well at that point. We had the eye elevated, and the forehead corrected, but with the progress of time there was still a residual downward displacement of the inner canthus and the lower lid of the left eye relative to globe level.

In other words, the release of the downward pressures from the brain with resulting displacement of the globe still did not allow a catch-up growth process to occur in the maxilla and inferior orbit.

(slide) Accordingly, the eyelids themselves had to be adjusted and the canthi modified and positioned before we could get what we thought was a reasonably finally corrected solution at six years of age. This was a big improvement over the original situation, even though it required three operations instead of only one.

What conclusions should we come to in treating a child with a similar deformity, in the light of what we have heard today? It seems to tell us that *we must start the surgical corrections as early as surgically practical*. Early operation will avoid the need for later, larger operations. Overcorrections of bony contours are sometimes desirable, in the mandible particularly, but they are not always desirable in other facial bones. The dural influence I just illustrated is an example of that. Secondary deformities may be arrested or minimized by early surgical treatment, but "catch-up growth" in already distorted, but relatively normal, adjacent areas is usually not sufficient to bring that part back to normal shape and size without further surgical intervention. We have seen a number of examples of this. Finally, multiple surgical stages are still usually required for major craniofacial deformities, but each operation is generally highly rewarding to the patient, to the family and to the surgeon.

The effect of surgical treatment on growth may be the most important current question in the emerging subspeciality of craniofacial surgery. Dr. Murray's group should be congratulated for attacking this important problem in such a constructive way.

DR. M. JUDAH FOLKMAN (Boston, Massachusetts): Dr. Murray's career has always amazed me, because after he saw to it that kidney transplantation was safely under way, he then embarked on the even more difficult endeavor of craniofacial surgery; and it has been very inspiring to watch him and his colleagues perfect this area of surgery and to achieve such extraordinary results as you saw this afternoon.

Craniofacial surgery has now reached a position of central importance in the Department of Surgery at Children's Hospital, and, in fact, it plays a most valuable role in the teaching of surgery at Children's. You might ask why should a branch of plastic surgery that at first glance seems so rarefied and so superspecialized; why should it have such a profound influence on the life of a university teaching hospital?

Well, one reason is that residents from other specialties who work beside Dr. Murray transfer these techniques and the judgments to their own fields, whether they be otolaryngologists or neurosurgeons or anesthetists or the general surgical resident caring for a trauma patient at night. All of these men and women return to their own work with greater competence, and in this sense plastic surgery continues to enrich the rest of the field.

Here is Dr. Murray, truly a master surgeon, but he himself always is learning in the presence of his students and residents. And I overheard him only a month or so ago say: "Now I'm really beginning to understand the forces that work on these congenital anomalies."

Finally, most surgeons are slightly uncomfortable taking on a patient who will need years of care and many sequential operations. But Dr. Murray and his colleagues have learned to support these patients, not only physiologically, but psychologically, and these patients and their parents are, I think, the most appreciative we have ever seen. His example is not lost on our younger associates.

DR. JOSEPH E. MURRAY (Closing discussion): I purposely avoided a technical presentation before this audience. However, I agree with Dr. Edgerton on his caveats about the difficulty in avoiding both the overcorrections and undercorrections. He has also wisely stressed the other unknown future problems.

Dr. Paul Greeley sent me a thoughtful letter after he saw the program. If I may, Mr. President, I would like to add Dr. Greeley as a fourth discussant by quoting his letter in part.

"I have heard by the grapevine that the procedure"—namely, craniofacial surgical correction—"has fallen into disrepute in the larger hospitals of the Chicago area, not because of the need for the operation, but because the operative time taken for each individual case is too long. It ties up operating rooms for several hours. Hence, the general surgeons have held back for space for their shorter cases. What about it?"

In response to Dr. Greeley, I admit that these operations do require six to ten hours' operating time. However, with increasing experience and a well functioning team of surgeons, anesthetists and nurses we have shortened our operative time almost by half for most of these procedures. Our group is indebted to Dr. Folkman at the Children's Hospital and to Drs. Moore and Mannick, my chiefs at the Peter Bent Brigham Hospital, for recognizing our needs and helping obtain sufficient operating time for these patients. The volume of patients is increasing steadily and the needs are great.

It has been a fun experience planning and executing these operations. The operations are only one stage in the care of these complex patients. The psychiatric aspects have enriched us tremendously. When we look at these patients and their families and all the interrelationships with school, peers and society, the overview changes completely. It becomes a whole new ball game which has added tremendously to the richness of our surgical experience.

Congenital Diaphragmatic Hernia

New Concept in Management

STEPHEN J. SHOCHAT, M.D., RICHARD L. NAEYE, M.D., W. D. A. FORD, M.B., F.R.C.S., VICTOR WHITMAN, M.D., M. JEFFREY MAISELS, M.D.

The newborn infant with a congenital diaphragmatic hernia (CDH) who develops severe respiratory distress requiring operative repair within the first 24 hours of life represents one of the most challenging problems in pediatric surgery. The mortality in these infants still exceeds 50% and has historically been attributed to ventilatory insufficiency secondary to pulmonary hypoplasia. However, the primary abnormality in these neonates seems to be an increase in pulmonary vascular resistance with an elevation of pulmonary artery pressure, right–left ductal shunting, preductal shunting and progressive hypoxemia. Eighteen neonates with a CDH were operated upon within the first 24 hours of life with a mortality of 38%. In no instance did ventilatory insufficiency seem to be a major factor in the death of the patient. Seven infants with progressive hypoxemia were treated with a vasodilator, tolazoline. Six of the seven infants showed an initial response to treatment, with a rise in preductal Pa_{O_2} and a decrease in ductal shunting. Four of these seven desperately ill neonates survived. Pathologic examination of the pulmonary vasculature in the nonsurvivors revealed an increase in muscle mass within the pulmonary arterioles. An exaggerated vasoconstrictive response of an abnormally hypertrophied pulmonary vascular bed leading to an elevation of pulmonary vascular resistance, rather than abnormalities of ventilation, appears to be the important mechanism leading to the often fatal hypoxemia observed in the neonate with a CDH. Improved survival will depend upon the successful management of the deranged pulmonary vascular hemodynamics seen in these infants.

From the Division of Pediatric Surgery,
Department of Surgery,
Stanford University Medical Center,
Stanford, California and the Departments of Surgery,
Pathology and Pediatrics,
The Milton S. Hershey Medical Center,
Pennsylvania State University, Hershey Pennsylvania

THE NEWBORN INFANT with a congenital diaphragmatic hernia (CDH) who develops severe respiratory distress requiring operative repair within the first 24 hours of life represents one of the most challenging problems in pediatric surgery. Despite improved surgical techniques, anesthetic management, postoperative respiratory care and intensive care facilities, the mortality in these infants has not changed appreciably over the past decade and, as reported in several recent series, still exceeds 50%.[5,7,21] This high mortality, which is usually due to progressive hypoxemia, has historically been attributed to ventilatory insufficiency secondary to pulmonary hypoplasia. However, the primary abnormality in these neonates, as pointed out by Dibbins and Weiner[4] and Collins et al.[2], seems to be a persistence of a fetal type of circulation, with an increase in pulmonary vascular resistance, elevated pulmonary artery pressure and right–left ductal and preductal shunting leading to progressive hypoxemia. During the past four years, 18 infants under 24 hours of age were operated upon for repair of a CDH at the Milton S. Hershey Medical Center and the Stanford University Medical Center. A high pulmonary vascular resistance with right–left ductal and preductal shunting was the major pathophysiological alteration observed in the neonates with progressive hypoxemia. Improved survival of these infants will depend upon the successful management of this pulmonary vascular hemodynamic abnormality.

Clinical Data

Eighteen neonates with a CDH were operated upon in the first 24 hours of life between April 1975 and March 1979 (Table 1). There were seven deaths, a mortality of 38%. The first baby in this series developed a contralateral pneumothorax while being transported. He required resuscitation in the neonatal intensive care unit and died immediately following surgical repair. The next three deaths occurred early in our series, prior to the use of vasodilators, and did not receive op-

---

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

Reprint requests: Stephen J. Shochat, M.D., Chief, Division of Pediatric Surgery, Department of Surgery, Stanford University Medical Center, Stanford, California 94305.

0003-4932/79/0900/0332 $01.00 © J. B. Lippincott Company

TABLE 1. *Clinical Data and Blood Gas Analyses*

				Preoperative						Postoperative							
Case	Age* (hr)	Birth Wt (g)	Apgar (1 min)	Site	FI_{O_2}	pH	Pa_{CO_2} (Torr)	PaO_2 (Torr)	AaD_{O_2}† (Torr)	Site	FI_{O_2}	pH	Pa_{CO_2} (Torr)	PaO_2 (Torr)	AaD_{O_2} (Torr)	ΔPaO_2° (Torr)	Outcome
1	6	3850															Dead
2	22	3204	9	Cap	0.32	7.45	22.5	62		Cap	0.32	7.46	29	80			Alive
3	2	2700	3	UA	1.0	7.09	58.2	32	622	TA	1.0	7.26	43	43	627	7	Dead
4	6	2300	1	UA	1.0	6.84	88.0	32	593	TA	1.0	7.31	43	56	614	15	Dead
5	7	2750		UA	1.0	6.83	86.0	37	590	TA	1.0	7.40	32	125	556	61	Dead
6‡	10	3260	7	TA	1.0	7.15	50.6	86	576	TA	1.0	7.48	26	366	321	103	Alive
7‡	11	3544	8	UA	1.0	7.02	79.2	54	579	TA	1.0	7.38	42	360	311	280	Alive
8‡	14	3440	5	UA	0.6	7.10	65.4	52		RA	1.0	7.42	30	297	386	214	Alive
9	16	1956	6	UA	0.5	7.34	40.8	63		UA	0.4	7.36	40	105			Alive
10	7	3830	6	UA	1.0	6.94	98.6	58	556	TA	1.0	7.25	48	407	258	43	Alive
11	16	3180	9	UA	0.4	7.24	39.6	38		TA	0.56	7.45	34	201			Alive
12	10	3345	4	UA	0.4	7.40	31.0	36		RA	0.85	7.44	25	337			Alive
13	10	2700	6	UA	1.0	7.28	46.0	55	612	TA	0.53	7.40	35	219			Alive
14‡	6	2110	8	UA	1.0	6.76	100.0	36	577	TA	1.0	7.30	37	318	358	271	Dead
15‡	7	3000	2	RA	1.0	7.20	61.0	60	592	RA	1.0	7.36	34	346	333	268	Alive
16‡	6	3130	1	TA	1.0	7.32	34.0	85	594	RA	1.0	7.41	28	207	478	150	Dead
17	18	3000	7	UA	0.4	7.35	36.0	174		RA	0.40	7.37	39	186			Alive
18‡	7	4200	4	RA	1.0	7.38	35.0	490	188	RA	1.0	7.49	28	372	313	157	Dead

Cap = capillary; UA = umbilical artery; TA = temporal artery; RA = right radial artery; ΔPaO_2 = difference between preductal and postductal PaO_2 at an FI_{O_2} of 1.0.

* Birth to operation.

† Alveolar–arterial difference in partial pressure of oxygen at an FI_{O_2} of 1.0 ($AaD_{O_2} = 760 - [PaO_2 + PaCO_2 + 47]$).

‡ Infants who received tolazoline.

timum postoperative support. Seven infants were treated with a vasodilator, tolazoline, due to an increase in pulmonary vascular resistance with progressive hypoxemia. Four of these desperately ill neonates survived.

The infants who died were younger and in more distress and were slightly smaller, as indicated by the mean values for age, birth weight and Apgar score (Table 2). However, there is considerable overlap within each group. Associated congenital cardiac anomalies or other associated anomalies were not seen in this group of infants.

Caution must be used when comparing the mean preoperative and postoperative blood gas data (Table 2), since the management of these children varied greatly as a better understanding of the pathophysiology evolved. There is also great individual variability within each group. The postoperative blood gases recorded were those obtained shortly after operative repair or after the patient was stabilized in the immediate postoperative period.

Except for Case 18, all patients who died and the four patients who survived following tolazoline therapy had preoperative $Pa_{CO_2} > 60$ torr or $AaD_{O_2} > 500$ torr. This blood gas picture is a bad prognostic indicator, as Raphaely and Downes had no survivors with a pre-

TABLE 2. *Mean Values (Range) of Clinical Data and Blood Gas Analysis*

					Preoperative			Postoperative			
	No.	Age (hr)	Birth Weight (g)	Apgar (1 min)	$PaCO_2$ (Torr)	AaD_{O_2} (Torr)	PaO_2/FI_{O_2}	$PaCO_2$ (Torr)	AaD_{O_2} (Torr)	PaO_2/FI_{O_2}	ΔPaO_2 (Torr)
Alive	11										
Without tolazoline	7	14 (7–22)*	3030 (1956–3830)	6.7 (4–9)	44.9 (22.5–98.6)		162 (55–435)	40 (25–48)		364 (250–465)	
With tolazoline	4	10 (7–14)	3311 (3000–3544)	5.5 (2–8)	64.0 (50.6–79.2)	582 [3]† (576–592)	71 (54–86)	33 (26–42)	337 (311–386)	342 (297–366)	216 (103–280)
Dead	7										
Without tolazoline	4	5 (2–7)	2900 (2300–2850)	2.0 [2] (1–3)	77.4 [3] (58.2–88.0)	601 [3] (590–622)	33 [3] (32–37)	39 [3] (32–43)	599 [3] (556–627)	75 [3] (43–125)	27 [3] (7–61)
With tolazoline	3	6 (6–7)	3146 (2110–4200)	4.0 (1–8)	56.0 (34–100)	453 (188–594)	203 (36–490)	31 (28–37)	383 (313–478)	299 (207–372)	192 (150–271)

* Range.

† Number of infants studied.

operative AaD_{O_2} greater than 500 torr[21], and Dibbins and Weiner had only one survivor with an initial Pa_{CO_2} greater than 60 torr.[4] Elevated initial postoperative Pa_{CO_2} was not seen in any of the patients who died, ruling out ventilatory insufficiency with CO_2 retention as a major factor in mortality. Excluding Case 1, only two patients who died failed to show an improvement in postoperative oxygenation (Cases 3 and 4). Postoperative AaD_{O_2} revealed various degrees of preductal shunting. However, the mean postoperative AaD_{O_2} of the three deaths in the tolazoline group compares favorably with the survival group, indicating that these infants were potentially salvageable. The Pao_2/Fi_{O_2} ratio was determined since many of the infants who survived without tolazoline did not receive an Fi_{O_2} of 1.0. The mean preoperative values are low in all groups. However, those patients who survived without tolazoline had a higher Pao_2/Fi_{O_2} ratio than the other groups, if Case 18, in which the patient died with tolazoline, is excluded from this group (mean, 60). The postoperative mean Pao_2/Fi_{O_2} ratios are comparable between the patients that survived and those who died following tolazoline therapy, again suggesting that these children are salvageable. The postoperative ΔPao_2 indicated a significant right–left ductal shunt in all patients receiving tolazoline and in one infant who died early in the series without tolazoline (Case 5). Two patients who survived without tolazoline (Case 10 and Case 13) had preoperative $Pa_{CO_2} > 60$ or $AaD_{O_2} > 500$; however, they did not have significant right–left ductal shunts postoperatively and did not develop progressive hypoxemia.

The seven patients who received tolazoline followed similar clinical courses. All, except Case 18, had a predicted poor prognosis ($Pa_{CO_2} > 60$ torr or $AaD_{O_2} > 500$) and were monitored by measuring simultaneous preductal and postductal arterial blood gases. An initial improvement in the Pao_2 was seen following surgery; however, a marked right–left ductal shunt was present or appeared in the immediate postoperative period. Clinical deterioration as manifested by progressive hypoxemia ensued, presumably due to increasing pulmonary arterial resistance. Six of the seven patients showed an initial response to tolazoline, with a rise in preductal Pao_2 and a decrease in ductal shunting. The one patient who did not respond to tolazoline died. Three infants became refractory to this drug despite increasing concentrations, and two of these infants died.

There were several complications associated with the use of tolazoline. Hypotension, tachycardia and a decreased urine output were seen in four infants. Minor episodes of gastrointestinal bleeding occurred in four patients. Two infants had unexplained seizures while receiving tolazoline. There were also two cardiac arrhythmias that may have been associated with tolazoline infusion, and one infant became thrombocytopenic.

All of the survivors are doing well without respiratory symptoms or neurologic deficits up to three years following operative repair. Many of the infants who received tolazoline had prolonged high preductal Pao_2; however, there were no cases of retrolental fibroplasia.

The pulmonary vasculature of the patients in Cases 14 and 16 were studied pathologically and were found to contain an increased muscle mass when compared to age-matched controls.[18]

Details of the clinical course of three infants who received tolazoline are described.

Case Reports

Case 6. A 3260 g male infant of 36 weeks gestational age, was born with mild respiratory distress and cyanosis. A chest x-ray revealed a left diaphragmatic hernia. A nasogastric tube and endotracheal tube were inserted, and he was transferred to the Milton S. Hershey Medical Center. Blood gases with manual ventilation and an Fi_{O_2} of 1.0 showed pH, 7.15; Pa_{CO_2}, 50.6; Pao_2, 86. A left diaphragmatic hernia was repaired at ten hours of age with creation of a ventral hernia and insertion of a left chest tube which was placed to 10-cm negative suction. A small hypoplastic left lung was seen at the time of surgery. Blood gases immediately after reduction revealed pH, 7.48; Pa_{CO_2}, 26; Pao_2, 366. Postoperatively he was placed on continuous positive airway pressure with an Fi_{O_2} of 1.0. Repeat blood gases showed a temporal artery pH of 7.28; Pa_{CO_2}, 23; Pao_2, 212. (Umbilical artery pH, 7.33; Pa_{CO_2}, 36; Pao_2, 109.) Blood pressure was 72/42. The Fi_{O_2} was decreased and his condition was stable four hours postoperatively with a pH of 7.39; Pa_{CO_2}, 32; Pao_2, 118. A gradual deterioration in blood gases without response to increasing Fi_{O_2} followed, and tolazoline, 2 mg/kg/hour, was begun 24 hours postoperatively. Marked improvement in the temporal artery Pao_2 occurred six hours following initiation of infusion, but a right–left ductal shunt was present. At 32 hours postoperatively, no ductal shunt was noted, and the Fi_{O_2} was decreased. Due to hypotension and a decreased urine output, tolazoline was gradually decreased and discontinued. He was extubated on postoperative day four. Chest x-rays revealed gradual expansion of the left lung over the next seven days. Ventral hernia repair was performed on the 25th postoperative day. The remainder of his hospital course was uneventful. Eye examination was normal, without evidence of retrolental fibroplasia. He is now well, without pulmonary symptoms three years following surgery (Fig. 1).

Case 14. A 2110 g female infant of 34 weeks gestational age, presented with respiratory distress at birth. An endotracheal tube was inserted, and a chest x-ray was taken which confirmed the diagnosis of a left diaphragmatic hernia. She was transferred to the Stanford University Medical Center, and initial blood gases following manual ventilation at an Fi_{O_2} of 1.0 revealed pH, 6.76; Pa_{CO_2}, 100; Pao_2, 36. Tolazoline, 5 mg had been given intravenously prior to transfer. A left diaphragmatic hernia was repaired, and a small extralobar sequestration was resected. Due to a large diaphragmatic defect, a muscle flap was used for closure and a ventral hernia was constructed. A chest tube was placed in the left thoracic cavity and connected to 10 cm H_2O negative suction. Postreduction intraoperative blood gases from a temporal artery catheter at an Fi_{O_2} of 1.0 revealed pH, 7.51; Pa_{CO_2}, 40; Pao_2, 221. There was a marked right–left ductal shunt (umbilical artery Pao_2, 76). She was placed on assisted ventilation with a peak inspiratory pressure of 40 cm H_2O, end expiratory pressure of 3 cm H_2O and a rate of 60. Temporal artery blood gases on an Fi_{O_2} of 1.0 showed a pH of 7.21; Pa_{CO_2}, 36; Pao_2, 233. The right–left ductal shunt persisted with an umbilical artery Pao_2 of 47. A right chest tube was inserted and con-

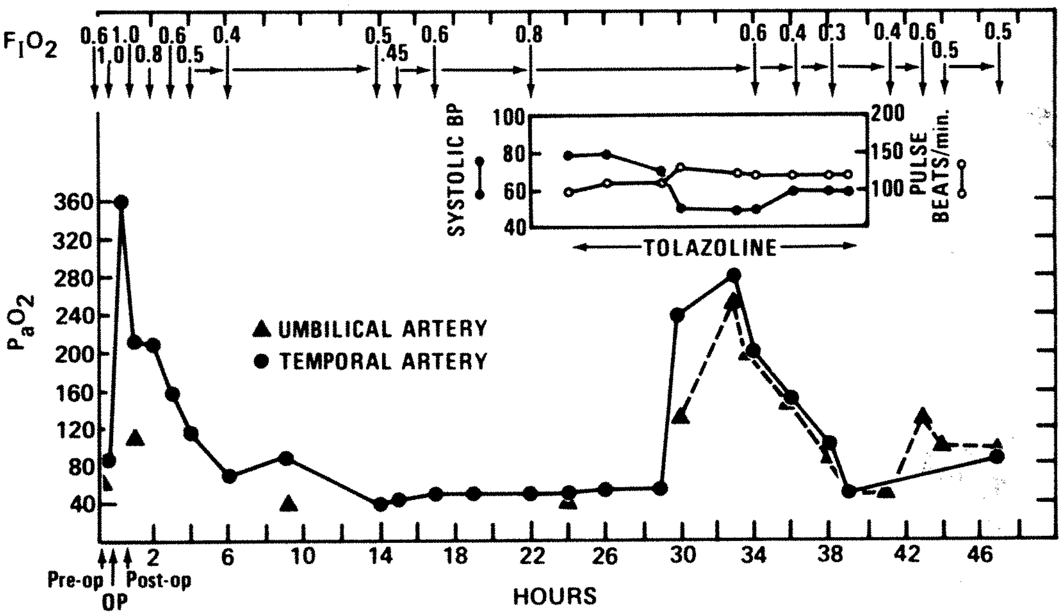


FIG. 1. Clinical course and response of patient in Case 6 to tolazoline. Note episode of hypotension and tachycardia associated with tolazoline infusion.

nected to 10 cm negative suction. Preductal oxygenation improved during the immediate postoperative period, but a metabolic acidosis persisted and an episode of hypotension was treated with volume expansion. Blood gases at eight hours postoperatively from the temporal artery line revealed a pH of 7.30, Pa_{CO_2} of 37 and PaO_2 of 318 at an FI_{O_2} of 1.0. (Umbilical artery PaO_2, 47). She gradually became more hypoxemic, and a tolazoline infusion, 2 mg/kg/hour, was begun 13 hours postoperatively. There was no response to tolazoline, despite an increase in the dosage to 4 mg/kg/hour. Progressive hypoxia, hypercarbia and acidosis ensued. She was given dopamine, glucagon and Dilantin® without success and died 31 hours postoperatively. An autopsy was performed and was unremarkable, except for a hypoplastic left lung. The pulmonary vasculature was studied, and a significant increase in muscle mass was seen (Fig. 2). The mean muscle mass (area arterial media/area intimal nuclei) was 5.5 ± 2.5 compared to that in an age-matched control of 3.91 ± 2.79.[18]

Case 15. A 3000 g, term male infant developed severe respiratory distress shortly after birth, requiring endotracheal intubation. A chest x-ray revealed a left diaphragmatic hernia. He was transferred to the Stanford University Medical Center, where initial blood gases from a right radial artery catheter revealed a pH of 7.2, Pa_{CO_2} of 61 and PaO_2 of 60 following mechanical ventilation at an FI_{O_2} of 1.0. A left diaphragmatic hernia was repaired at seven hours of age. A small hypoplastic left lung was seen, and a chest tube was placed with 8 cm H_2O negative pressure. Mechanical ventilation was begun postoperatively with a peak inspiratory pressure of 30 cm H_2O, end expiratory pressure of 4, a rate of 40/min and an FI_{O_2} of 1.0. A right chest tube was inserted. Radial artery blood gases revealed pH, 7.36, Pa_{CO_2}, 34; PaO_2, 346; however, there was a marked right–left ductal shunt (umbilical artery PaO_2, 78). The FI_{O_2} was gradually decreased to 0.80 but had to be increased to 1.0 at eight hours postoperatively due to progressive hypoxia. (Radial artery pH, 7.45; Pa_{CO_2}, 28; PaO_2, 86.) Hypoxemia persisted, and a tolazoline infusion, 2 mg/kg/hour, was begun, with a marked improvement in blood gases. (Radial artery pH, 7.44; Pa_{CO_2}, 32; PaO_2, 329; umbilical artery PaO_2, 269.) The tolazoline infusion was accidentally discontinued for one hour, resulting in a

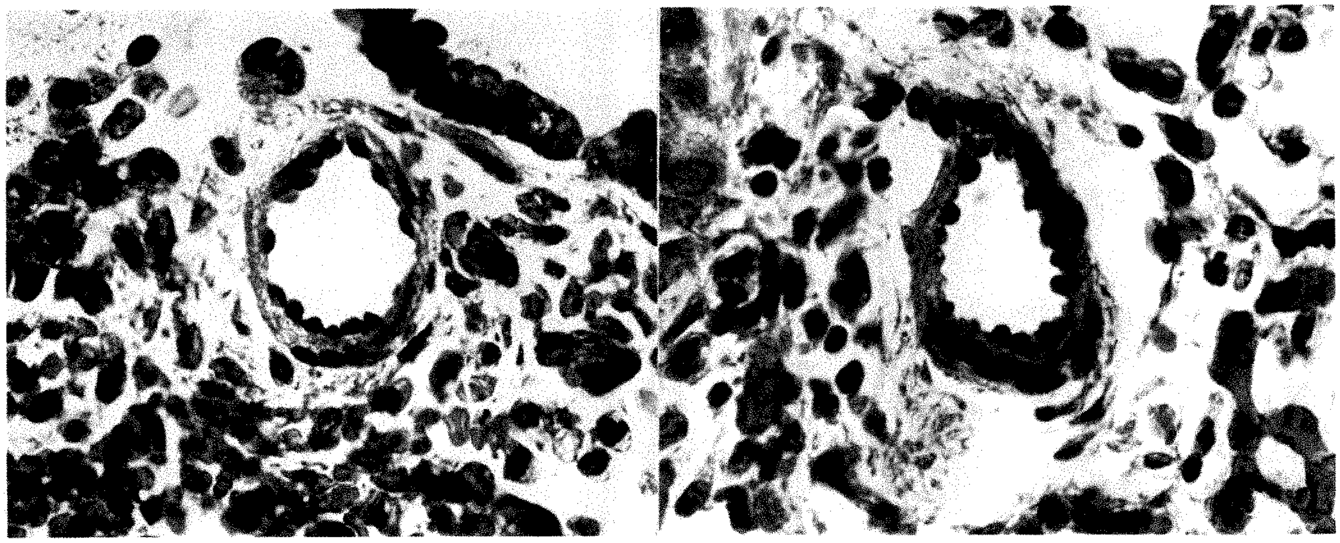


FIG. 2. Increased muscle mass within pulmonary arteriole of patient in Case 14 (B) as compared to an age-matched control (A).

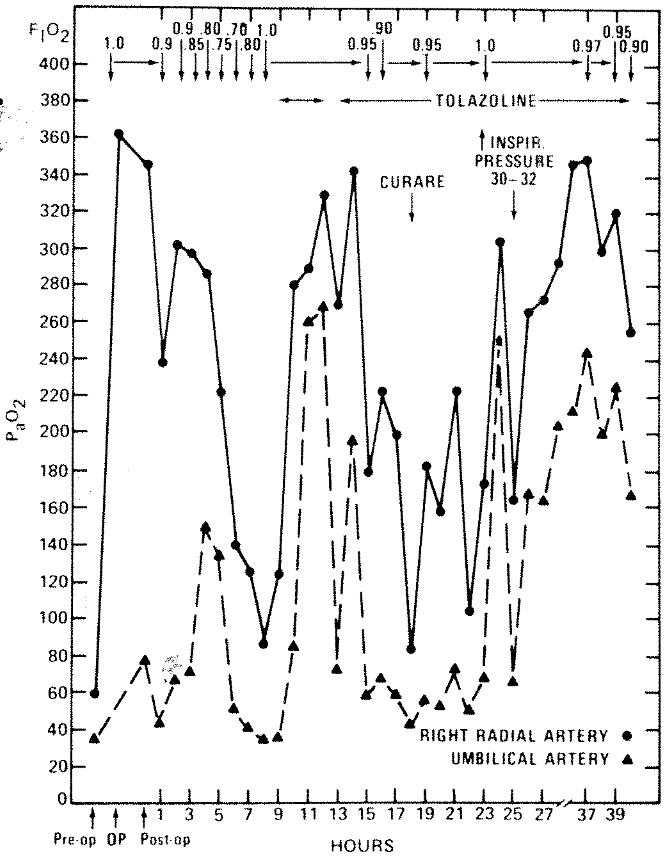


FIG. 3. Clinical course of Case 15. Note the influence of $F_{I_{O_2}}$ variations, tolazoline, curare and an increased inspiratory pressure on oxygenation.

marked right–left ductal shunt (radial artery Pao_2, 269; umbilical artery Pao_2, 73). The infant again became severely hypoxic when the $F_{I_{O_2}}$ was decreased to 0.90 but improved slightly following 1 mg of curare intravenously. Hypoxia recurred, and the tolazoline infusion was increased to 3 mg/kg/hour, with a striking improvement in blood gases. (Radial artery pH, 7.49; Pa_{CO_2}, 28 Pao_2, 303; umbilical artery pH, 7.49; Pa_{CO_2}, 30; Pao_2, 250.) His condition again deteriorated but responded to an increase in the peak inspiratory pressure to 32 cm H_2O. Despite a significant and persistent right–left ductal shunt, he was able to tolerate decreasing $F_{I_{O_2}}$ over the next 24 hours (Fig. 3). No significant right–left shunt was present by the fourth postoperative day. Tolazoline was gradually decreased and was discontinued on the seventh postoperative day. He was difficult to wean from the ventilator; however, he is now doing well at home with mild tachypnea 6 months postoperatively. Presently his chest x-ray reveals expansion of the left lung with mild overexpansion of the right.

Discussion

Pathologic examination of the lungs of infants who have died with CDH reveals a decrease in size and weight, with the ipsilateral lung being the smaller and showing a distorted distribution of segmental airways. The airways are decreased in both lungs due to a reduction in the small bronchi and bronchioli. The reduction of total lung volume is due to a reduced total number of alveoli as a result of this deficiency in bronchiolar generation. These pathologic findings have lead to the assumption that the high mortality seen following repair of a diaphragmatic hernia is due to pulmonary hypoplasia. However, despite a reduction in total lung volume, the contralateral lung in infants with CDH usually is able to maintain ventilation. Our series of cases tends to support this observation, as initial postoperative CO_2 retention suggesting ventilatory insufficiency was not seen in any of the fatalities. In surviving infants, the small hypoplastic ipsilateral lung eventually expands and fills the thoracic cavity. Hislop and Reid have shown that the lungs of infants who survive following repair of a CDH expand by increasing the size of the alveoli while maintaining a normal rate of multiplication.[11] Total lung volume is normal, but there is an abnormal distribution, with the ipsilateral lung contributing only 40%. Pulmonary function studies performed on children who have had CDH repaired as infants confirm the above observations in that total lung capacity and vital capacity are normal.[25] However, a consistent abnormality seen in all patients studied by xenon radiospirometry was a reduced blood flow to the lung on the side of the hernia.

The strongest argument against the theory that pulmonary hypoplasia and ventilatory insufficiency contribute to the mortality in CDH is the common clinical pattern that is usually seen in those neonates dying following repair of a diaphragmatic hernia. There is a marked improvement in oxygenation in the immediate postoperative period, followed by deterioration 12–24 hours postoperatively, with progressive hypoxemia, acidosis, hypercarbia and death, despite all therapeutic manipulations. Four of our seven deaths followed this clinical course.

Murdock et al.[17] and Rowe and Uribe[22] were the first to measure simultaneous preductal (temporal or radial artery) and postductal (umbilical artery) Pao_2s in infants with CDH. They showed that there were large alveolar–arterial oxygen tension differences between the radial or temporal artery and descending aorta in the presence of adequate alveolar ventilation as measured by normal Pa_{CO_2}. They suggested that in addition to intrapulmonary shunting and shunting across the foramen ovale there must be relatively large volumes of venous admixture through the ductus arteriosus. Subsequent clinical studies of neonates with CDH were carried out by Dibbins and Weiner[4] and Collins et al.,[2] and the major role of the pulmonary circulation in determining the outcome of these infants was stressed. Using paired arterial samples drawn above and below the ductus, evidence of preductal and ductal right–left shunting was demonstrated. Postoperative improvement was associated with a decrease in both preductal and ductal shunting, while episodes of clinical deterioration could be identified as severe progressive hypoxemia accompanied by preductal shunting.

Cardiac catheterization studies have been performed in children with CDH and demonstrate pulmonary arterial hypertension with a right–left shunt across the ductus, elevated right ventricular end diastolic pressure and elevated right atrial pressure with shunting across the foramen ovale. Pulmonary angiography shows a decreased total pulmonary flow with shunting across the ductus and almost no perfusion of the lung on the side of the diaphragmatic hernia.

The pulmonary vasculature of infants who have died with CDH has been investigated. Naeye et al found a significant increase in muscle mass in the small pulmonary arteries in ten of 12 children with CDH when compared to age-matched controls.[18] In each infant with a diaphragmatic hernia, the muscle values were almost identical in the two lungs. Levin has confirmed this finding and also found that there was a decrease in the total size of the pulmonary vascular bed, as well as a decrease in the number of vessels per unit of lung.[12]

The abnormally large mass of muscle within the small pulmonary arteries in infants with CDH is present at birth and is probably associated with various degrees of intrauterine fetal distress or hypoxia. This muscular hypertrophy could also develop as a result of mechanical distortion of the fetal ductus arteriosus due to the mediastinal shift caused by the diaphragmatic hernia. Partial constriction of the ductus would increase the pulmonary blood flow through a smaller than normal vascular bed, resulting in pulmonary hypertension, which has been shown to cause excessive pulmonary arterial smooth muscle in fetal lambs.[12] The degree of muscle hypertrophy may depend upon the timing of the intrauterine events leading to the development of the diaphragmatic hernia and could explain the variable clinical course seen in infants following operative reduction. The observation that there is an inverse relationship between pulmonary arterial muscle mass and relative lung weights would tend to support this theory.[18]

This anatomically abnormal pulmonary vascular bed in infants with CDH is capable of an exaggerated response to factors which produce pulmonary vasoconstriction in the newborn period. There are numerous factors that affect pulmonary vascular tone (Fig. 4). The interaction of these various factors probably plays a major role in initiating the increase in pulmonary vascular resistance which results in the progressive hypoxemia and high mortality following repair of a CDH.

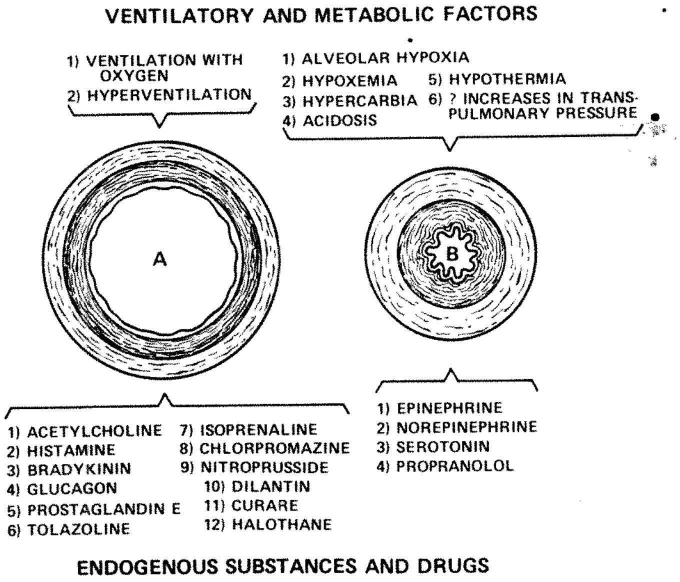


FIG. 4. Factors that affect pulmonary vascular tone. A) Vasodilatation, decreased pulmonary arterial resistance, increased pulmonary blood flow; B) vasoconstriction, increased pulmonary arterial resistance, decreased pulmonary blood flow.

Alveolar hypoxia is one of the most potent stimuli leading to pulmonary vasoconstriction, and a large muscle mass in the pulmonary arterioles seems to enhance this pressor response.[6] Alveolar hypoxia is certainly present preoperatively in the neonate with CDH and probably persists in the ipsilateral lung postoperatively, despite expansion of the contralateral lung. The hypoplastic lungs of the fetal lamb have been found to have a reduced compliance, and inflation pressures of 35 cm H_2O or more are required to open alveoli.[23] Alveolar hypoxia could also explain why seemingly small reductions in the F_{IO_2} of infants following repair of a CDH are frequently followed by an increase in right–left shunting, presumably due to pulmonary vasospasm, despite the presence of a normal PaO_2. This observation has frequently been seen in our patients postoperatively (Fig. 3). The etiology of pulmonary arteriolar vasoconstriction secondary to alveolar hypoxia is not known, but vasoactive substances or a reflex mechanism may be involved. Alveolar hypoxia may also have a direct vasospastic effect on the arterioles.

Hypoxemia can cause pulmonary vasospasm, and this effect can be seen independent of alveolar hypoxia.[6] Acidosis, hypercarbia and hypothermia are also associated with pulmonary vasoconstriction and increased pulmonary vascular resistance. The relative effects of hypoxemia and acidosis in producing pulmonary arteriolar vasoconstriction are not clear but are most likely synergistic. An increase in transpulmonary pressure has recently been shown to be associated with hypoxemia and respiratory insufficiency in newborn puppies.[20] While pulmonary artery pressures were not measured, it was inferred that increased transpulmonary pressure could initiate pulmonary arteriolar vasoconstriction leading to progressive hypoxemia.

The exact role played by pulmonary vascular volume, pulmonary blood flow and the ductus arteriosus in children with CDH is not clearly understood. The infant with a CDH and a normal blood volume must force most of the right ventricular output through the contralateral pulmonary vascular bed until the ipsilateral lung expands. This leads to an overdistended unilateral pulmonary circulation with elevated pulmonary arterial, right ventricular end diastolic and right atrial pressures. In addition, there is a diminished cross-sectional area of the vascular bed due to an increase in musculature, compounded by pulmonary vasoconstriction. The end result is severe desaturation of the systemic circulation due to massive right–left shunting across the ductus and foramen ovale. Dibbins and Weiner feel that the ductus serves as a vent, preventing right ventricular failure until relaxation of the pulmonary vascular bed occurs with expansion of the ipsilateral lung.[4] The ductus, however, can shunt enough desaturated blood into the systemic circulation to produce hypoxemic tissue acidosis, which will increase pulmonary vasoconstriction. This fact has lead to the suggestion by Collins et al. that the ductus arteriosus should be ligated in infants with progressive hypoxemia following repair of CDH.[2] They believe this will increase pulmonary blood flow and pulmonary artery pressure with an improvement in peripheral oxygenation, the patent foramen ovale protecting against right heart failure. There is some evidence that increased pulmonary blood flow can relieve the vasoconstriction associated with hypoxia[1]; however, the clinical results of ductus ligation without pharmacologic lowering of the pulmonary vascular resistance have not been encouraging.[2]

Regardless of the roles played by pulmonary blood flow and the ductus arteriosus, the main concern in these infants is the relief of pulmonary vasoconstriction and a decrease in pulmonary vascular resistance. High negative intrathoracic pressures on the ipsilateral side should be avoided due to the possible vasoconstrictive effects of increased transpulmonary pressure. Improving ventilatory mechanics by hyperventilation and providing high inspiratory oxygen concentrations will help relieve alveolar hypoxia, hypoxemia, acidosis and hypercarbia. A contralateral chest tube should be inserted prophylactically. Peckham and Fox have shown the validity of hyperventilation in infants with the clinical syndrome of persistent fetal circulation, a condition pathophysiologically similar to that of the infant with a CDH, by monitoring pulmonary artery pressure during treatment.[19] The pulmonary arterial pressures fell in all patients with a decrease in pulmonary vascular resistance, a decrease in AaD_{O_2} and improved oxygenation. Mechanical ventilation with high inflating pressures and high rates were maintained to control the Pa_{CO_2} in the 25–30 mmHg range. If a large right–left ductal shunt or preductal shunt persists after satisfactory ventilation is established, as determined by a normal Pa_{CO_2} and pH, then pharmacologic measures to lower pulmonary vascular resistance will be required. There were no survivors in the present series with large postoperative preductal or ductal shunts who did not receive pharmacologic support with tolazoline.

Many endogenous substances and drugs affect pulmonary vascular tone,[14] as depicted in Figure 4. Acetylcholine has been used with some success in children with CDH but must be infused through a pulmonary artery catheter, as it is neutralized rapidly in the blood stream. Chlorpromazine has been tried by Dibbins with a satisfactory response in one surviving infant.[3] Curare seems to be beneficial by increasing effective ventilation due to increased chest wall compliance as well as by releasing histamine, which is a pulmonary vasodilator in man[13] (Fig. 3). Halothane has been shown to inhibit the vasoconstrictive response of alveolar hypoxia but has not been studied clinically. Dilantin, nitroprusside and glucagon have also been used experimentally to dilate the pulmonary vascular bed. However, tolazoline is the drug that has been used most extensively in the treatment of the clinical syndrome of persistent fetal circulation[8,13,24] and has recently been used successfully in neonates with CDH.[15,16]

Tolazoline is primarily an alpha adrenergic blocking agent; however, it also has a direct nonadrenergic relaxant effect on vascular smooth muscle. Tolazoline also has a direct inotropic effect on the heart, which is mediated through histamine receptors. It is chemically related to the sympathomimetic amines and histamine. Seven neonates were treated with tolazoline because of progressive hypoxemia following repair of a CDH. Six infants showed an initial response to an infusion of 2 mg/kg/hour (Figs. 1 and 3), and four infants survived. Three infants showed an initial response but became refractory to increasing concentrations, up to 8 mg/kg/hour. Two of these infants died due to progressive hypoxemia and acidosis, and one infant survived after a prolonged period of hypoxemia. These cases of tachyphylaxis associated with the use of tolazoline are not uncommon. The infant who showed no response to tolazoline received a bolus infusion prior to operative repair, which may have been related to her failure to respond postoperatively; however, this infant also had a persistent metabolic acidosis. Autopsy in this child revealed a significant increase in pulmonary arteriolar muscle mass (Fig. 2).

Several complications were associated with the use of tolazoline, which is consistent with the experience of others who have noted a high complication rate.[24] Hypotension, tachycardia and decreased urine output were frequent complications. Hypotension can usually be treated with blood volume expansion; however, pharmacologic support may be required. Gastrointestinal bleeding was seen and is thought to be due to increased gastric secretion secondary to the histamine-like action of tolazoline. The episodes of gastrointestinal bleeding were mild and were controlled by conservative means. Thrombocytopenia, seizure activity and cardiac arrhythmias were also seen and may have been related to tolazoline therapy. None of the above complications contributed directly to the mortality seen in these infants. While tolazoline may effectively lower the pulmonary vascular resistance in neonates with CDH, careful and continuous monitoring of these infants is required as potentially fatal complications are associated with its use.

An agent that may have potential usefulness in children following repair of CDH is prostaglandin E_1 (PGE_1). Experimentally, PGE_1 inhibits the pulmonary vascular pressor response to hypoxia and can reduce the pulmonary hypertension caused by prostaglandin F_2. Prostaglandin E_1 has been used clinically to manage the critically ill neonate with ductus dependent cyanotic congenital heart disease with few complications. Pyrexia, peripheral vasodilation, tremors and mild focal seizures have been reported.[9] One patient who showed a striking improvement in oxygenation after receiving PGE_1 was later found to have a closed ductus. The improved oxygenation was thought to be due to a reduction in the pulmonary vascular resistance by PGE_1.[9]

Several animal models have been developed in order to study the hemodynamic and ventilatory changes that are associated with CDH.[10,23] Increased pulmonary artery pressures, decreased perfusion of the ipsilateral lung at birth, varying degrees of right–left shunting and decreased lung compliance have been demonstrated. However, these studies have been disappointing to date due to their inability to consistently reproduce the clinical situation which is usually encountered following repair of a CDH.

The rapid pathophysiological changes that occur postoperatively in these infants require constant observation and continuous monitoring of various parameters. Until recently, it was not possible to continuously monitor the rapid changes that were occurring in Pao_2 following repair of a CDH. However, the development of the transcutaneous oxygen electrode will enable continuous monitoring of preductal and postductal Pao_2 in the critically ill infants, so that therapeutic decisions can be made early prior to significant clinical deterioration. Another recent advance that will aid in the management of neonates with CDH is the development of a small, flow-directed, balloon-tipped catheter which can be placed in the pulmonary artery without requiring cardiac catheterization. Continuous monitoring of pulmonary artery pressure should be helpful in determining the efficacy of various therapeutic modalities.

The clinical data presented in this report and the abundant pathologic and physiologic data that have been gathered in recent years clearly emphasize the important role played by the pulmonary vasculature in the survival of neonates with CDH. An exaggerated vasoconstrictive response of an abnormally hypertrophied pulmonary vascular bed leading to an elevation of the pulmonary vascular resistance appears to be the important mechanism leading to the often fatal hypoxemia seen in these neonates. A better understanding of the initiating factors leading to this deranged pathophysiology is imperative and, hopefully, will be aided by the design of more appropriate animal models.

The investigation and development of more effective and safer pharmacologic agents capable of reversing pulmonary arteriolar vasoconstriction will facilitate the successful management and improve the survival of these critically ill infants.

Acknowledgment

We wish to thank Kathleen Gifford, R.N., and Karen McKinley, R.N., for their help in collecting the clinical data and Ms. Linda Watkins for her excellent secretarial assistance. We would also like to thank Dr. A. W. Dibbins for his helpful suggestions concerning the pathophysiology of these neonates and all the nursing and resident staff who devoted so much of their time to the care of these infants.

References

1. Benumoe, J. L. and Wahrenbrock, E. A.: Blunted Hypoxic Pulmonary Vasoconstriction by Increased Lung Vascular Pressures. J. Appl. Physiol., 38:846, 1975.
2. Collins, D. L., Pomerance, J. J., Travis, K. W. et al.: A New Approach to Congenital Posterolateral Diaphragmatic Hernia. J. Pediatr. Surg., 12:149, 1977.
3. Dibbins, A. W.: Neonatal Diaphragmatic Hernia: A Physiologic Challenge. Am. J. Surg., 131:408, 1976.
4. Dibbins, A. W. and Weiner, E. S.: Mortality From Neonatal Diaphragmatic Hernia. J. Pediatr. Surg., 9:653, 1974.
5. Ehrlich, F. E. and Salzberg, A. M.: Pathophysiology and Management of Congenital Posterolateral Diaphragmatic Hernias. Am. Surg., 44:26, 1978.
6. Fishman, A. P.: Hypoxia on the Pulmonary Circulation: How and Where It Acts. Circ. Res., 38:221, 1976.
7. Fitzgerald, R. J.: Congenital Diaphragmatic Hernia: A Study of Mortality Factors. Ir. J. Med. Sci., 146:280, 1977.
8. Goetzman, B. W., Sunshine, P., Johnson, J. D. et al.: Neonatal Hypoxia and Pulmonary Vasospasm: Response to Tolazoline. J. Pediatr., 89:617, 1976.
9. Graham, T. P., Jr., Atwood, G. F. and Boucek, R. J., Jr.: Pharmacologic Dilatation of the Ductus Arteriosus With Prostaglandin E_1 in Infants with Congenital Heart Disease. South. Med. J., 71:1238, 1978.

10. Haller, J. A., Jr., Signer, R. D., Golladay, E. S. et al.: Pulmonary and Ductal Hemodynamics in Studies of Simulated Diaphragmatic Hernia of Fetal and Newborn Lambs. J. Pediatr. Surg., 5:675, 1976.
11. Hislop, A. and Reid, L.: Persistent Hypoplasia of the Lung After Repair of Congenital Diaphragmatic Hernia. Thorax, 31:450, 1976.
12. Levin, D. L.: Morphologic Analysis of the Pulmonary Vascular Bed in Congenital Left-Sided Diaphragmatic Hernia. J. Pediatr., 92:805, 1978.
13. Levin, D. L., Heymann, M. A., Kitterman, J. A. et al.: Persistent Pulmonary Hypertension of the Newborn Infant. J. Pediatr., 89:626, 1976.
14. Levin, D. L., Cates, L., Newfeld, E. A. et al.: Persistence of the Fetal Cardiopulmonary Circulatory Pathway: Survival of an Infant After a Prolonged Course. Pediatrics, 56:58, 1975.
15. Levy, R. J., Rosenthal, A., Freed, M. D. et al.: Persistent Pulmonary Hypertension in a Newborn with Congenital Diaphragmatic Hernia: Successful Management With Tolazoline. Pediatrics, 60:740, 1977.
16. Moodie, D. S., Telander, R. L., Kleinberg, F. and Feldt, R. H.: Use of Tolazoline in Newborn Infants With Diaphragmatic Hernia and Severe Cardiopulmonary Disease. J. Thorac. Cardiovasc. Surg., 75:725, 1978.
17. Murdock, A. I., Burrington, J. B. and Swyer, P. R.: Alveolar to Arterial Oxygen Tension Difference and Venous Admixture in Newly Born Infants with Congenital Diaphragmatic Herniation Through the Foramen of Bochdalek. Biol. Neonate, 17:161, 1971.
18. Naeye, R. L., Shochat, S. J., Whitman, V. and Maisels, M. J.: Unsuspected Pulmonary Vascular Abnormalities Associated With Diaphragmatic Hernia. Pediatrics, 58:902, 1976.
19. Peckham, G. J. and Fox, W. W.: Physiologic Factors Affecting Pulmonary Artery Pressure in Infants With Persistent Pulmonary Hypertension. J. Pediatr., 93:1005, 1978.
20. Ramenofsky, M. L.: The Effects of Intrapleural Pressure on Respiratory Insufficiency. Presented at the 10th Annual Meeting of the American Pediatric Surgical Association, 1979.
21. Raphaely, R. C. and Downes, J. J., Jr.: Congenital Diaphragmatic Hernia: Prediction of Survival. J. Pediatr. Surg., 8:815, 1973.
22. Rowe, M. I. and Uribe, F. L.: Diaphragmatic Hernia in the Newborn Infant: Blood Gas and pH Considerations. Surgery, 70:758, 1971.
23. Starrett, R. W. and deLorimier, A. A.: Congenital Diaphragmatic Hernia in Lambs: Hemodynamic and Ventilatory Changes with Breathing. J. Pediatr. Surg., 10:575, 1975.
24. Stevenson, D. K., Kasting, D. S., Darnall, R. A. et al.: Refractory Hypoxemia Associated With Neonatal Pulmonary Disease: The Use and Limitations of Tolazoline. J. Pediatr., submitted for publication.
25. Wohl, M. E. B., Griscom, N. T., Strieder, D. J. et al.: The Lung Following Repair of a Congenital Diaphragmatic Hernia. J. Pediatr., 90:405, 1977.

DISCUSSION

DR. LESTER WARREN MARTIN (Cincinnati, Ohio): We also have used tolazoline, or Priscoline, in some of our infants with diaphragmatic hernia. Our problem is evaluating our results to determine whether the baby would have become well without it. To try to determine this, we have placed our infants in three simple categories.

One is a group with normal blood gases. We feel those babies should get well without Priscoline. The second group consists of those infants with abnormal blood gases that can be corrected by mechanical ventilation. We feel those infants are also potentially salvageable without the aid of other agents.

The third group is the infants with abnormal preoperative blood gases that cannot be corrected with mechanical ventilation. These are the infants who, in our experience, have all died. There is evidence to indicate that their problem is persistent fetal circulation. The pulmonary vascular resistance forces the blood to continue going through the ductus, bypassing the lungs. Theoretically, the Priscoline should produce pulmonary vasodilation and permit the flow of blood through the pulmonary vascular bed. Priscoline, however, also causes peripheral vasodilation with a resultant undesirable fall of systemic pressure. Some have advocated administration of Priscoline directly into the pulmonary artery by way of a small Swan-Ganz type catheter. Ligation of the ductus has also been suggested, but temporary occlusion of the ductus in two of our infants resulted in significant bradycardia and systemic hypotension.

I wish to ask Dr. Shochat if any of the Priscoline-treated survivors had preoperative acidosis which could not be corrected by mechanical ventilation. If so, then Priscoline would appear to be of significant value.

DR. J. ALEX HALLER, JR. (Baltimore, Maryland): Three years ago we had a workshop in the Surgical Section of the Academy of Pediatrics on diaphragmatic hernia in an attempt to collate our clinical experience throughout the country, and I thought it might be helpful to review quite briefly with you some of those points of discussion, because I realize that many of you are not constantly dealing with this problem.

(slide) One of the most important aspects of Dr. Shochat's presentation is the focus on why we are losing 50% of the babies born with a hole in the diaphragm, because we certainly have the operative techniques to correct it. In perspective, a baby who lives longer than 48 hours with a diaphragmatic defect will survive in almost 100% of the situations.

Babies less than 24 hours old who have severe respiratory distress have a frustratingly high mortality rate (50%).

In our workshop many of the principles which Dr. Shochat outlined were discussed, and some of the recommendations which he presented were also outlined. I believe that he is the first to report the use of some of those techniques.

(slide) When we evaluated the clinical results around the country, several important points were obvious. First, as Dr. Shochat has pointed out, we were not losing these babies because they had inadequate pulmonary function or inadequate tissue. There were a few who died of lethal abnormalities. One of the striking features of this particular congenital abnormality is that it is usually isolated. Therefore, if we could help these children, we would be dealing with an otherwise perfectly normal child with an excellent life expectancy.

The second point was that intrathoracic tension and compression were responsible for underdevelopment of the lung. A few children had insufficient lung tissue, but they could always be detected, because it was impossible, in spite of good ventilation, to lower their Pa_{CO_2}'s. Thus, as Dr. Martin has indicated, we are able to identify a group of patients who demonstrate progressive hypoxemia and acidosis. The real question is: What is wrong with them, and why do we have this continuing loss?

(slide) A few may fit into this category of mechanical problems in the lung, with rupture, hyperinflation, etc.; but it seems to be primarily this problem of persistent fetal circulation, with right-to-left shunting at both the level of the patent foramen ovale and the patent ductus.

(slide) For those of you who have not thought about fetal circulation for a while, you may recall that as the blood returns in the fetus to the right atrium, it is shunted both through the foramen ovale and also through the ductus arteriosus. The neonatologists are now calling this condition, in which there is a failure of relaxation of the pulmonary vascular bed, persistent fetal circulation. This appears to be the primary problem.

(slide) There are ways of approaching this experimentally, and a number of us have been working at creating a congenital diaphragmatic hernia model.

(slide) When you do this, it is possible to show hypoplasia of the lung. You can even ligate the left pulmonary artery, but in none of those preparations do we have a persistence of the fetal circulatory status in the lung.

(slide) As Dr. Shochat has indicated, we do not yet know what the developmental anomaly is which accompanies the diaphragmatic defect in a number of these patients. The question is: Should we be looking for other approaches? Should we consider the possibility of ligating the ductus arteriosus, recognizing, of course, that we would overload the right ventricle immediately? Could we be more aggressive about the use of ionotropic agents to support the failure of the right ventricle, and thus get some of these babies through, and stop their right-to-left shunting? Are there better drugs available than Priscoline, as Dr. Shochat has indicated?

I would like, therefore, to close my comments by asking him just those questions. Is there a better vasodilator? Are he and his group experimenting with other drugs that seem to be better than the tolazoline?

Secondly, is it proper for us to consider the possibility of ligating the patent ductus arteriosus, but using aggressive techniques to support right ventricular function?

Dr. James A. O'Neill (Nashville, Tennessee): I congratulate Dr. Shochat for emphasizing the usefulness of this pulmonary vasodilator in a situation that is critical, in infants who are ordinarily not only symptomatic on the first day of life, but usually symptomatic within the first six to eight hours, or even immediately. He has also emphasized and demonstrated the effectiveness of this.

The problem, of course, that he also mentioned, is the matter of the inconsistency of response. Some infants will respond very well, and others will go into a refractory state.

(slide) I would like to show you something that Dr. Shochat mentioned in passing. This is an example of a single infant symptomatic immediately at birth, and you'll see the pH and blood gasses outlined before you. This infant started out with a conventional dose of tolazoline, and very rapidly this had to be doubled. This was continued for over five days. The infant became partially refractory as demonstrated on this slide. As one examines the course of the Po_2, one can see that, on a variable basis, there was a refractory situation. Shunt fractions were calculated frequently. You will note from the course of the gases that periodic doses of d-tubocurarine not only provided better ventilation, but also repeatedly reversed the shunt. I emphasize that because there has been some recent enthusiasm expressed for methyl curare, that is, Metubine, which does not have a histaminic effect. It may very well be that this is an important adjunct to the treatment of such infants.

We have come to use this routinely in situations like this. I would ask Dr. Shochat whether he has any enthusiasm for the routine use of curare as well as priscoline in an infant who is critical or whether he does this on a sporadic basis.

Dr. Stephen J. Shochat (Closing discussion): I will first discuss the question of when to begin tolazoline therapy.

Tolazoline is a potentially dangerous drug associated with several complications, including hypotension, gastrointestinal bleeding, seizures and thrombocytopenia. Because of these complications, we usually try to stabilize the patients and establish satisfactory ventilatory mechanics before we use this drug. If a significant right to left ductal shunt exists or preductal shunting persists, tolazoline therapy is begun.

We believe there may be a better drug to use. My cardiologist colleagues have suggested another pulmonary vasodilator, prostaglandin E_1, as they have been using this drug successfully for the treatment of ductus-dependent, cyanotic congenital heart disease. We are going to think about the early use of prostaglandin E_1 in these particular patients.

We do use curare as a routine, Dr. O'Neill, and we think it is important not only because the babies can be better controlled on the ventilator, but also because of its possible histamine-like effects.

(slide) The clinical course of this baby helps to answer Dr. Martin's question as to when to use tolazoline. This infant did not respond to tolazoline and we probably should have used the drug much earlier. We started at this juncture, and the baby never did respond. The time to use a vasodilator is when the babies are first noted to be shunting, either across the ductus or preductally. This baby also had evidence of hypovolemia and acidosis, which are important factors that must be dealt with in these children.

While I would now recommend using prostaglandin E_1 in infants with a marked right to left shunt across the ductus or preductally, tolazoline should be effective if used carefully and judiciously.

(slide) Not all the babies with poor preoperative blood gases will necessarily shunt postoperatively. Here is a baby that was critically ill prior to surgical treatment but in the postoperative period did not have a major right to left shunt, either preductally or ductally. She went on to do quite well without any pharmacologic support and is now doing fine.

The children that have survived after tolazoline therapy have not developed chronic pulmonary disease. (slide) Here is the first patient we treated with tolazoline. He is now doing quite well without any respiratory symptoms, a little over three years postoperatively.

The Fibrinolytic System

A Key to Tumor Metastasis?

J. M. MALONE, M.D., S. L. WANGENSTEEN, M.D., W. S. MOORE, M.D., K. KEOWN, M.A.

Neither histologic nor clinical staging reliably correlates with patient survival or the time course of tumor metastatic spread. There is no general biologic tumor marker which is able to distinguish those patients with microscopic residual cancer who may benefit from adjuvant anticancer treatment from those patients cured by their primary treatment who do not require additional anticancer therapy. Our data suggest that tumor activation and inhibition of fibrinolysis are related to the likelihood of tumor spread. Calculation of mean activation/inhibition ratios (A/I ratios) in groups of tumors with and without metastatic spread demonstrated a statistically significant difference between their respective A/I ratios ($p < 0.001$). In addition, the mean activation/inhibition ratios for secondary or "metastatic" lesions were significantly different from the mean activation/inhibition ratios of the original tumors from which they metastasized ($p < 0.001$). Therefore, tumor activation/inhibition ratios would appear to have clinical reliability as biologic markers for the presence or absence of tumor metastases. These data may have important therapeutic implications that would permit the use of activation/inhibition ratios as a biologic marker for the presence or absence of tumor spread at the time of primary surgical excision of the tumor. These observations warrant further investigation into the mechanisms of tumor interaction with the fibrinolytic system.

From the Department of Surgery, University of Arizona College of Medicine, Tucson, Arizona

HISTOLOGIC AND CLINICAL STAGING correlate poorly with survival and the time course of tumor metastatic spread. The phenomena of dormancy, spontaneous regression and the appearance of widespread metastases after "curative" resection of Stage I or Stage II lesions emphasizes the difficulty in using histologic staging to predict biological tumor growth, metastatic spread and patient survival. Anticancer treatment is based upon norms for tumor cell types rather than a special knowledge of the behavior of an individual lesion. A biologic tumor marker is needed to accurately assess tumor growth or recurrence. To a limited extent and for specific tumors the carcinoma embryonic antigen and the alpha fetoprotein have provided assessment of the adequacy of tumor resection and of tumor recurrence. However, there is no general biologic tumor marker which is able to distinguish those patients with microscopic residual cancer who will develop tumor recurrence and who therefore require adjuvant anticancer treatment from those patients cured as a result of their primary treatment and who therefore do not require additional anticancer therapy. Tumor metastases have been correlated with both activation and inhibition of the fibrinolytic system.[4,10,15-18,20,24] We report here the results of our investigation of the phenomena of tumor activation and inhibition of fibrinolysis as a potential biological marker for the presence or absence of metastatic disease.

Materials and Methods

Biopsies of both normal tissue and tumor were obtained from fresh surgical specimens of patients undergoing curative or palliative tumor resection at the Tucson V.A. Hospital from January 1, 1978 to January 1, 1979. When possible, biopsies were taken from the tumor, normal tissue around the tumor and normal tissue at the surgical margins of resection. All tissue samples were transported to our research laboratory in normal saline, and warm ischemia time was limited to 1 hour. All tissue specimens were cryopreserved and were analyzed in bimonthly batches.[15] The techniques of cryopreservation have previously been published and will not be reviewed in this report.[15]

A standardized fibrin plate technique was used to

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

Sponsored in part by Veterans Administration Career Development Grant 678-544701 and Veterans Administration Grant 622-579803.

Reprint Requests: James M. Malone, M.D., Department of Surgery, A.H.S.C., Tucson, Arizona 85724.

0003-4932/79/0900/0342 $00.90 © J. B. Lippincott Company

measure tissue activation of fibrinolysis.[5,15] Thirty milligrams of human fibrinogen (Merck, Sharp and Dohme, West Point, PA) were dissolved in sodium barbital buffer and precipitated with six units of bovine thrombin in a 100 mm Petri dish. These plates are stable for three weeks at 4° and for approximately 48 hours at 37°. Tissue activation of fibrinolysis was measured by placing a 7 mm punch biopsy of tissue, cross-sectional surface down, in the center of the fibrin plate and then incubating the plate at 37° for 24 hours. Tissue fibrinolytic activator activity was terminated by adding 10 cc of 1.0% trichloroacetic acid to the fibrin plate after completion of incubation. The zones of fibrinolysis were quantitatively measured with an electronic planimeter (Lasico, Model 1250 E) and expressed in square millimeters. An example of tissue activation of fibrinolysis is shown in Figure 1.

A modified fibrin plate technique, developed in our laboratory and previously described, was used to measure tissue inhibition of fibrinolysis.[15] Fifteen milligrams of human fibrinogen (Calbiochem) were dissolved in sodium barbital buffer and precipitated with six units of bovine thrombin in a 100 mm Petri dish. These plates demonstrate spontaneous lysis at both 4° and 37°. Tissue inhibition of fibrinolysis was measured by placing a 7 mm punch biopsy of tissue, cross-sectional surface down, in the center of a plate and then incubating the plate at 37° until complete lysis of control plates (without tissue specimens) was noted. The incubation time averaged 8 hours. In the absence of tissue inhibition of fibrinolysis, tissue specimens were found floating freely in the dissolved fibrin. The presence of tissue inhibitors of fibrinolysis resulted in a zone of unlysed fibrin around the tissue specimen. The analysis was terminated on the test plates by the addition of 10 cc of 1.0% trichloroacetic acid. Areas of unlysed fibrin (inhibition of fibrinolysis) were quantitatively measured with an electric planimeter and expressed in square millimeters. An example of tumor inhibition of fibrinolysis is shown in Figure 2.

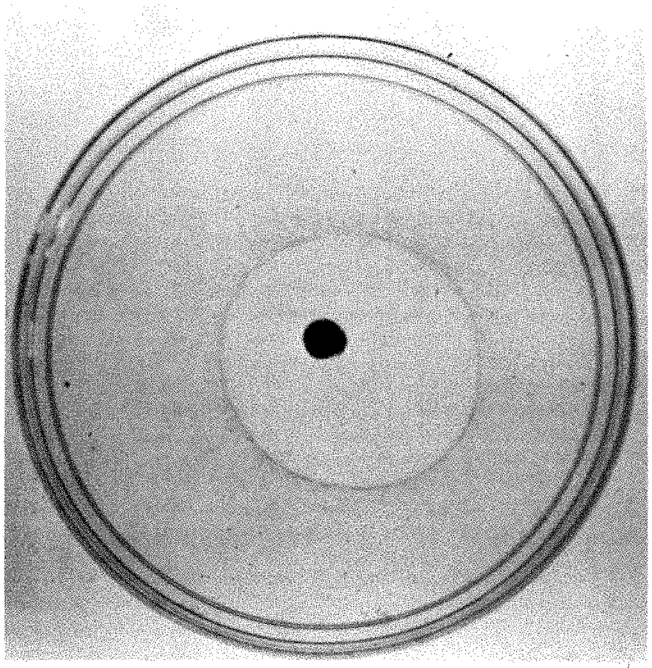


FIG. 1. Low-power view of a fibrin plate for measuring fibrinolytic activator activity. The zone of fibrinolysis around a specimen of normal lung is easily noted.

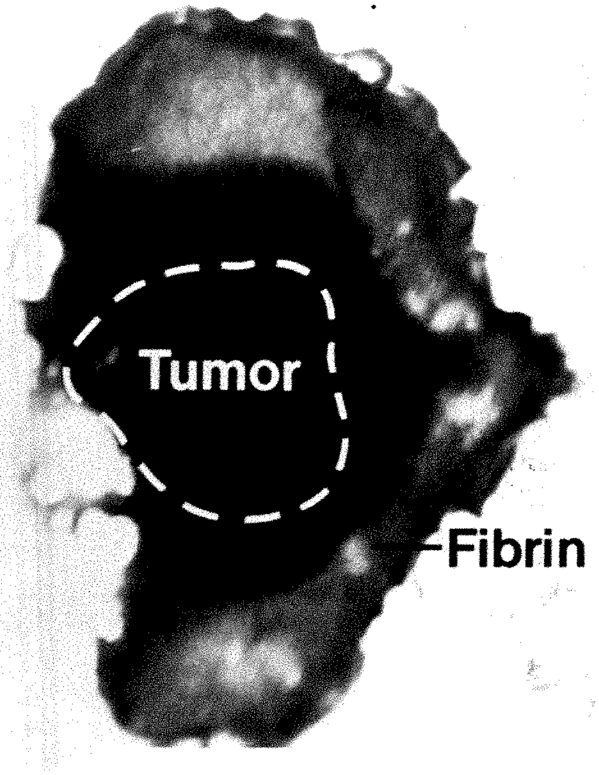


FIG. 2. High-power view of the central portion of a fibrin plate used for measuring inhibition of fibrinolysin. The zone of unlysed fibrin (inhibition of fibrinolysis) is readily apparent around a biopsy of adenocarcinoma of the colon.

Statistical analysis was performed using the Student's t-test for nonpaired means. All data were analyzed on a programmable electronic calculator (HP-97).

The gross and microscopic pathology in all tissue samples was reviewed by one of the authors (JMM).

Results

Biopsies of normal tissue, including specimens from most thoracic and abdominal organs, were analyzed for both activation and inhibition of fibrinolysis ($N = 38$). All normal tissue demonstrated activation of fibrinolysis (Table 1). The amount of fibrinolytic

TABLE 1. *Normal Tissue: Fibrinolytic Activity*

Tissue	No. Samples (N = 38)	Mean Activation (sq mm)	Mean Inhibition (sq mm)
Adrenal	2	481	0
Bone	1	837	0
Colon	4	798	0
Fat/subcutaneous	2	901	0
Gall bladder	1	60	0
Iliac vein	1	502	0
Inferior vena cava	1	160	0
Liver	2	27	64
Lymph node	2	561	0
Lung	4	924	0
Nerve	1	733	0
Parathyroid	1	470	0
Renal vein	1	273	0
Skeletal muscle	6	623	0
Skin	4	91	0
Spleen	3	220	0
Stomach	2	737	0

activity ranged from 27 sq mm (liver) to 924 sq mm (lung). Most normal tissue demonstrated only moderate amounts of fibrinolytic activator activity (200–600 sq mm), while bone, colon, subcutaneous fat, lung, nerve and stomach demonstrated high levels of fibrinolytic activator activity (>700 sq mm). No normal tissue other than liver (64 sq mm) demonstrated inhibition of fibrinolysis.

Several types of benign lesions were analyzed for both activation and inhibition of fibrinolysis (N = 14). All benign lesions demonstrated moderate activation of fibrinolysis (>200 sq mm); however, none of the benign lesions demonstrated inhibition of fibrinolysis. It is noteworthy that cirrhotic liver demonstrated increased activation and decreased inhibition of fibrinolytic activity (Table 2) compared to normal liver (Table 1). Two superficial melanomas are listed in Table 2 because the lesions, while histologically malignant, had been present for more than 10 years without evidence of spread.

Forty-three malignant neoplasms were studied: 17 tumors were primary neoplasms without metastases; 12 tumors were primary lesions with metastases; nine tumors were secondary or "metastatic"; and five tumors were lymphomas. All malignant neoplasms, except an astrocytoma and a sacral chordoma, demonstrated inhibition of fibrinolysis (range, 23–312 sq mm) (Tables 3–6). All malignant neoplasms, except an embryonal cell carcinoma, demonstrated activation of fibrinolysis (range, 12–1508 sq mm) (Tables 3–6). Grossly normal tissue around tumor failed to demonstrate inhibition of fibrinolysis but consistently demonstrated decreased fibrinolytic activator activity, ranging from 20–40% compared to normal tissue at the surgical margins of the same specimen ($p < 0.05$).

Histologically normal liver in patients with either extrahepatic or intrahepatic tumor demonstrated marked changes in hepatic fibrinolytic activity compared to normal liver in patients without tumor (Table 7).

Since there was an approximate linear correlation between increasing levels of activation of fibrinolysis and decreasing levels of inhibition of fibrinolysis and tumor metastatic spread, excluding lymphomas and secondary or "metastatic" tumors, activation/inhibition ratios (A/I ratios) were calculated for each tumor. Excluding those tumors previously mentioned, the A/I ratios had a linear correlation with tumor metastatic potential (Tables 3 and 4). With one exception, malignant neoplasms without metastatic spread had A/I ratios less than eight (Table 3). With one exception, malignant neoplasms with metastatic spread had A/I ratios greater than ten (Table 4). When we divided all malignant neoplasms, excluding lymphomas and secondary or "metastatic" tumors, into two subgroups based upon the presence or absence of metastatic spread and then calculated their respective A/I ratios, it was observed that tumors without metastases had a mean A/I ratio of 4.74 (Table 3) and that tumors with metastases had a mean A/I ratio of 19.98 (Table 4). The difference in mean A/I ratios for tumors with and without metastases is highly significant ($p < 0.001$).

The difference between the A/I ratios for primary tumors and their respective metastases was highly significant ($N = 5$, $p < 0.001$). The mean A/I ratio for all secondary or "metastatic" lesions was 1.52 (Table 5), significantly different from both the mean A/I ratio for tumors without metastases (A/I = 4.74, $p < 0.03$) and tumors with metastases (A/I = 19.98, $p < 0.001$).

The correlation between lymphoma stage and mean A/I ratio (Stage II, A/I = 22.94; Stage IV, A/I = 2.24) is shown in Table 6. While the difference between the A/I ratios for Stage II and Stage IV lesions is large, it is not statistically significant due to the small sample size.

Activation/inhibition ratios were not calculated for either benign lesions or normal tissue, since, other than liver, neither normal tissue nor benign lesions demonstrated inhibition of fibrinolysis (Tables 1 and 2).

TABLE 2. *Benign Lesions: Fibrinolytic Activity*

Tissue	No. Samples (N = 14)	Mean Activation (sq mm)	Mean Inhibition (sq mm)
Cirrhotic liver	3	438	0
Granulation tissue	1	359	0
Keloid	2	245	0
Scar	2	369	0
Splenic hemangioma	1	1105	0
Superficial melanoma	2	231	0
Villous adenoma	3	542	0

TABLE 3. *Primary Neoplasms Without Metastases: Fibrinolytic Activity*

Tissue	No. Samples	Mean Activation (sq mm)	Mean Inhibition (sq mm)	Activation/ Inhibition (A/I Ratio)
Astrocytoma	1	243	0	0.0
Sacral chordoma	1	123	0	0.0
Adenocarcinoma: colon	1	346	312	1.11
Adenocarcinoma: rectum	1	394	277	1.42
Adenocarcinoma: cecum	1	45	28	1.61
Squamous cell: trachea	1	147	74	1.99
Epidermoid carcinoma: bladder	1	192	81	2.37
Adenocarcinoma: colon	1	345	73	4.74
Adenocarcinoma: colon	1	658	121	5.44
Adenocarcinoma: cecum	1	364	64	5.69
Adenocarcinoma: cecum	1	214	35	6.11
Adenocarcinoma: cecum	1	342	55	6.22
Adenocarcinoma: cecum	1	369	58	6.36
Carotid body	1	518	76	6.82
Adenocarcinoma: colon	1	381	49	7.75
Hepatoma	1	687	87	7.90
Meningioma	1	677	45	15.04
	N = 17	$\bar{M} = 356$	$\bar{M} = 84$	$\bar{M} = 4.74$

Discussion

The data from this study demonstrated that with the exception of normal liver the presence of tissue inhibition of fibrinolysis was consistent with a diagnosis of malignancy. Metastatic tumor spread appeared to correlate directly with activation of fibrinolysis and inversely with inhibition of fibrinolysis. With one exception, malignant neoplasms without metastatic spread had A/I ratios less than eight (Table 3). With one exception, neoplasms with metastatic spread had A/I ratios greater than ten (Table 4). The difference in mean A/I ratios for tumors with metastases (A/I = 19.98) and tumors without metastases (A/I = 4.74) is highly significant ($p < 0.001$). It would thus appear that tumor A/I ratios have statistically reliable predictive value for the presence or absence of tumor metastatic spread.

An overview of our data which might explain the relationship between tumor metastasis formation and the fibrinolytic system would be the following: At the primary tumor level, fibrinolytic activator activity is associated with tumor cell shedding; at the individual tumor cell level, fibrinolytic inhibitory activity is associated with tumor cell endothelial adherence and subsequent tumor metastasis formation. If these theoretical considerations are correct, then one would expect that successful tumor metastatic lesions would demonstrate both decreased activation of fibrinolytic activity and increased inhibition of fibrinolytic activity compared to their respective primary tumors. These were the exact findings of this study. Secondary or "metastatic" lesions exhibited decreased fibrinolytic activator activity and increased fibrinolytic inhibitory activity compared to their respective primary or "parent" tumors ($p < 0.001$). In addition, the overall mean A/I ratio for secondary or "metastatic" tumors (A/I = 1.52) is significantly different from the mean

TABLE 4. *Primary Neoplasms with Metastases: Fibrinolytic Activity*

Tissue	No. Samples	Mean Activation (sq mm)	Mean Inhibition (sq mm)	Activation/ Inhibition (A/I Ratio)
Squamous cell: lung	1	98	38	2.58
Melanoma	1	812	75	10.83
Adenocarcinoma: stomach	1	829	60	13.82
Adenocarcinoma: colon	1	640	38	16.86
Osteosarcoma: arm	1	691	40	17.28
Adenocarcinoma: breast	1	858	47	18.26
Adenocarcinoma: breast	1	767	37	20.72
Adenocarcinoma: breast	1	1319	63	20.94
Adenosquamous: oropharynx	1	1105	52	21.25
Adenosquamous: oropharynx	1	768	31	24.76
Adenocarcinoma: colon	1	1034	33	31.30
Adenocarcinoma: breast	1	1508	33	41.26
	N = 12	$\bar{M} = 869$	$\bar{M} = 46$	$\bar{M} = 19.98$

TABLE 5. *Secondary Neoplasms (Metastatic Lesions): Fibrinolytic Activity*

Tissue	No. Samples	Mean Activation (sq mm)	Mean Inhibition (sq mm)	Activation/ Inhibition (A/I Ratio)
Embryonal cell carcinoma	1	0	174	0.0
Melanoma	1	23	305	0.08
Adenocarcinoma: pancreas	1	12	57	0.21
Adenocarcinoma: pancreas	1	40	123	0.33
Adenocarcinoma: pancreas	1	121	235	0.51
Adenocarcinoma: lung	1	319	246	1.29
Adenocarcinoma: pancreas	1	154	89	1.73
Adenocarcinoma: colon	1	544	250	2.18
Melanoma	1	403	55	7.33
	N = 9	$\bar{M}$ = 179	$\bar{M}$ = 170	$\bar{M}$ = 1.52

A/I ratio for both tumors without metastases (A/I = 4.74; $p < 0.03$) and tumors with metastases (A/I = 19.98; $p < 0.001$). The basis for the difference in A/I ratios between a collection of tumor cells as a primary lesion and a collection of the "same" tumor cells as a secondary or "metastatic" lesion is not explained by the data in this report.

Histologically normal liver in patients with either extrahepatic or intrahepatic tumor demonstrated dramatic changes in hepatic fibrinolytic activity compared to normal liver in patients without tumors (Table 7). Although the significance of these changes is unknown, it is exciting to suggest that they may be associated with the pathophysiology of successful tumor cell implantation and metastasis formation in the liver.

The significance of the changes in fibrinolytic activity demonstrated with lymphomas (Table 6) is unclear due to the small sample size analyzed in this study. Whether or not the correlation between stage of lymphoma and the A/I ratio is statistically valid will have to await the testing of more lymphoma specimens.

Our data are in accord with other reports. As early as 1956, Cliffton and Grossi, using a rabbit model, noted that activated plasmin significantly decreased both the thrombotic properties and the incidence of metastatic implantation of innoculated V2 carcinoma.[3] Subsequently, Grossi et al. (1960) demonstrated that pretreatment with fibrinolysin could decrease the incidence of metastases with VX-2 carcinoma, Brown-Pearce carcinoma and Walker 256 carcinosarcoma in various animal models.[8] More recent clinical studies support this earlier experimental data. Peterson et al. (1973) demonstrated that increased tumor fibrinolytic activity was associated with an increased incidence of lymph node metastases.[18] Newstead et al. (1976) reported that in patients with colorectal carcinoma the hematogenous spread of tumor cells (the number of tumor cells in peripheral blood and draining colonic veins) increased with increasing levels of tumor fibrinolytic activator activity.[17] Thornes (1975) reported a beneficial effect on patient survival in a controlled setting where warfarin was used as an adjunct to chemotherapy with disseminated lymphosarcoma, adenocarcinoma of the breast and adenocarcinoma of the ovaries.[20] In addition, Thornes has reported that streptokinase therapy as an adjunct to therapy for advanced carcinoma of the colon appeared to be of beneficial effect compared to surgery alone.[20] Finally, current tumor cell studies corroborate both the early experimental data and the recent clinical investigation. Christman et al. (1975) demonstrated that the tumorigenic capacity of murine melanoma in immunocompetent hosts correlated with tumor plasminogen activator production *in vitro*.[2] A similar correlation between tumor activity and plasminogen activation was noted by Mak et al. (1976) with androgen-dependent murine carcinoma[14] and by Freedman et al. (1974) in transformed cell lines in nude mice.[6] Jones et al. (1975) demonstrated that the introduction of murine sarcoma virus containing genes into TE-85 osteosarcoma was associated with both increased tumor fibrinolytic activity and tumorigenic capacity.[12] Similarly, Jones et al. (1975) demonstrated that the

TABLE 6. *Lymphomas: Fibrinolytic Activity*

Tissue	Stage	No. Samples	Mean Activation (sq mm)	Mean Inhibition (sq mm)	Activation/ Inhibition (A/I Ratios)
Liver: lymphoma	IV	1	150	120	1.25
Lymph node: histiocytic	IV	1	120	57	2.10
Spleen: lymphoma	IV	1	472	140	3.37
Lymph node: Hodgkins	II	1	393	39	10.08
Lymph node: histiocytic	II	1	1110	31	35.81

TABLE 7. *Normal Liver with Intrahepatic and Extrahepatic Tumor: Fibrinolytic Activity*

Tissue	No. Samples	Mean Activation (sq mm)	Mean Inhibition (sq mm)	Activation/ Inhibition (A/I Ratios)
Normal liver	2	27	6	0.42
Normal liver with extrahepatic tumor	2	0	167	0.0
Normal liver with intrahepatic tumor	2	470	426	1.10

cellular production of serine protease capable of activating plasminogen seemed to correlate with malignant transformation in wide ranges of cell lines transformed by several different agents.[11]

Review of both the clinical and experimental data which relate changes in tumor metastasis to the fibrinolytic sytem suggests that the mechanisms of action of anticoagulants, antiplatelet agents and fibrinolytic drugs with subsequent decreased incidence of tumor metastasis appear to include the following: 1) increased complement-dependent autocytotoxic tumor cell destruction[20,21]; 2) stimulation of cellular immune mechanisms (decreased blocking antigen)[9,20] with increased white cell mobility and white cell lysosomal activity[20,21]; 3) decreased tumor cell mobility[22]; 4) increased white cell aggregation[22]; 5) potentiation of cytotoxic agents[20]; 6) disruption of the fibrin platelet latticework that surrounds tumor cells and which appears to be necessary for tumor cell endothelial adherence and tumor cell invasion of the perivascular spaces[1,3,7,10,13,15,20,23-26]; and 8) enhancement of T lymphocyte/macrophage tumor cell recognition and destruction.[19]

Most of the malignant neoplasms evaluated in this report were adenocarcinomas of the gastrointestinal tract or breast. Due to small sample size, we cannot discuss the differences, if any, among adenocarcinomas, lymphomas, sarcomas, central nervous system tumors and primitive cell tumors with respect to either their intrinsic fibrinolytic activator or inhibitor activity. However, the preliminary data strongly suggest a valid relationship between all types of tumor metastases and the fibrinolytic system.

The fibrin plate assay used for tumor fibrinolytic activator activity in this report has been used extensively for the measurement of tissue fibrinolytic activator by several investigators, and therefore the assay has undergone reasonable scientific scrutiny with respect to both technique and reliability of results.[4,5,15] However, the same cannot be said for the assay we developed to measure inhibition of fibrinolysis. Our inhibitor assay has not yet been substantiated by other investigators. In addition, since the inhibitor assay uses an unstable fibrinogen which has a more rapid, spontaneous fibrinolytic activity than that of the tissue being analyzed, the assay measures relative inhibition of fibrinolysis, not absolute inhibitory activity. It is therefore impossible to know if we are measuring antiplasmins, antiplasminogens or a combination of fibrinolytic inhibitors. Nevertheless, the assay can be quantified. Excluding normal liver, inhibitory activity was noted only with malignant lesions. Based upon even a small sample size, the data are statistically significant. Obviously, the assay needs refinement, but the preliminary data suggest that further detailed investigation of tumor interaction with the fibrinolytic system is warranted.

Conclusion

Tumor activation and inhibition of fibrinolysis appears to be related to the pathology of tumor spread. Our data demonstrate a correlation between the incidence of tumor metastasis and both an increase in tumor fibrinolytic activator activity and a decrease in tumor fibrinolytic inhibitory activity. All but one malignant neoplasm without metastatic spread had activation/inhibition ratios of less than eight, while all but one tumor with metastatic spread had activation/inhibition ratios of greater than ten. Calculation of the respective mean activation/inhibition ratios of tumors with and without metastatic spread demonstrated a significant difference ($p < 0.001$). In addition, the activation/inhibition ratios for secondary or "metastatic" lesions differed significantly from the activation/inhibition ratios of the original or "parent" tumors from which they metastasized ($p < 0.001$). Therefore, tumor activation/inhibition ratios would appear to have statistical reliability as biological tumor markers for the presence or absence of metastatic tumor spread. These data have significant clinical and therapeutic implications and suggest that tumor activation/inhibition ratios may be used as biologic markers of tumor spread at the time of surgical excision of the tumor.

References

1. Agostino, D. and Cliffton, E. E.: Anticoagulants and the Development of Pulmonary Metastases: Anticoagulant Effect on Walker 256 Carcinosarcoma in Rats. Arch. Surg., 84:449–453, 1962.
2. Christman, J. K., Silagi, S. and Newcomb, E. W.: Correlated Suppression by 5-bromodeoxyuridine of Tumorigenicity and Plasminogen Activators in Mouse Melanoma Cells. Proc. Natl. Acad. Sci. USA, 72:47–50, 1975.
3. Cliffton, E. E. and Grossi, C. E.: Effect of Human Plasmin on the Toxic Effects and Growth of Blood Borne Metastases of the Brown-Pearce Carcinoma and the V-2 Carcinoma of the Rabbit. Cancer, 9:1147–1152, 1956.
4. Cliffton, E. E. and Grossi, C. E.: Fibrinolytic Activity of Human Tumors as Measured in the Fibrin Plate Method. Cancer, 8:1146–1154, 1955.

5. Franklin, J. D., Gervin, A. S., Bowers, D. B. et al.: Fibrinolytic Activator Activity in Human Neoplasms. Plast. Reconstr. Surg., 61:241–249, 1978.
6. Freedman, V. H. and Shin, S.: Cellular Tumorigenicity in Nude Mice: Correlation with Cell Growth in Semi-solid Medium. Cell, 3:355–359, 1974.
7. Gasic, G. J., Gasic, T. B., Galanti, N. et al.: Platelet Tumor Cell Interactions in Mice: The Role of Platelets in the Spread of Malignant Disease. Int. J. Cancer, 31:164–169, 1975.
8. Grossi, C. E., Agostino, D. and Clifften, E. E.: The Effect of Human Fibrinolysin on Pulmonary Metastases of Walker 256 Carcinosarcoma. Cancer Res., 20:605–608, 1960.
9. Holland, P. D. J., Browne, O. and Thornes, R. D.: The Enhancing Influence of Proteolysis on E-rosette Forming Lymphocytes (T Cells) in Vivo and in Vitro. Br. J. Cancer, 31:164–169, 1975.
10. Hoover, H. C., Jr. and Ketcham, A. S.: Techniques for Inhibiting Tumor Metastases. Cancer, 35:5–14, 1975.
11. Jones, P. A., Lang, W. E. and Benedict, W. F.: Fibrinolytic Activity in Human Fibrosarcoma Cell Line and Evidence for Induction of Plasminogen Activation Secretion During Tumor Formation. Cell, 6:245–252, 1975.
12. Jones, P. A., Rhim, J. S., Isaacs, H., Jr. et al.: The Relationship Between Tumorigenicity, Growth in Agar and Fibrinolytic Activity of Human Osteosarcomas. Int. J. Cancer, 16: 616–621, 1975.
13. Laki, K., Tyler, H. M. and Yancey, S. T.: Clot forming and Stabilizing Enzymes from Mouse Tumor YPC-1. Biochem. Biophys. Res. Commun., 24:776–781, 1966.
14. Mak, T. W., Rutledge, G. and Sutherland, D. J. A.: Androgen Dependent Fibrinolytic Activity in a Murine Mammary Carcinoma (Shionogi SC-115). Cell, 7:223–226, 1976.
15. Malone, J. M., Gervin, A. S., Keown, K. et al.: Tumor Interaction with the Fibrinolytic system. J. Surg. Res., in press.
16. Nagy, B., Ban, J. and Brodar, B.: Fibrinolysis Associated with Human Neoplasia. Production of Plasminogen Activator by Human Tumors. Int. J. Cancer, 19:614–620, 1977.
17. Newstead, G. L., Griffiths, J. D. and Salsbury, A. J.: Fibrinolytic Activity of Carcinoma of the Colorectum. Surg. Gynecol. Obstet., 143:61–64, 1976.
18. Peterson, H. I., Kjartansson, I., Korsan-Bengtsen, K. et al.: Fibrinolysis in Human Malignant Tumors. Acta Chir. Scand., 139:219–223, 1973.
19. Rosenthal, A. S., Blake, J. T., Ellner, J. J. et al.: Macrophase function in antigen recognition by T lymphocytes. *In* Nelson, D. (ed): Immunology of the Macrophage. New York, Academic Press, pp. 131–161, 1976.
20. Thornes, R. D.: Adjunct Therapy of Cancer Via the Cellular Immune Mechanism or Fibrin by Induced Fibrinolysis and Oral Anticoagulants. Cancer, 35:91–97, 1975.
21. Thornes, R. D., Deasy, P. F., Carroll, R. et al.: The Use of the Proteolytic Enzyme Brinase to Produce Autocytotoxicity in Patients with Acute Leukemia and Its Possible Role in Immunotherapy. Cancer Res., 32:280–284, 1972.
22. Thornes, R. D., Edlow, D. W. and Wood, S., Jr.: Inhibition of Locomotion of Cancer Cells, Granulocytes, Lymphocytes and Macrophages in Rabbits. Johns Hopkins Med. J., 123:306–317, 1968.
23. Wood, S., Jr.: Pathogenesis of Metastasis Formation Observed in Vivo in the Rabbit Ear Chamber. Arch. Pathol., 66:550–568, 1958.
24. Wood, S., Jr.: Experimental Studies of the Intravascular Dissemination of Ascitis V-2 Cancer Cells in the Rabbit with Special Reference to Fibrinogen and Fibrinolytic Agents. Bull. Schweiz. Akad. Med. Wiss., 20:92–121, 1964.
25. Wood, S., Jr., Holyoke, E. D. and Yardley, J. H.: Mechanisms of Metastasis Production by Blood Borne Cancer Cells. Can. Cancer Conf., 4:167–223, 1961.
26. Zeidman, I.: The Fate of Circulating Tumor Cells: 1. Passage of Cells through Capillaries, Cancer Res., 21:38–39, 1961.

DISCUSSION

DR. CARLO E. GROSSI (New York, New York): This work stresses the importance of the fibrinolytic mechanism in the spread of cancer cells, and I rise to discuss it because our interest dates back to when I was a resident and worked with Dr. Eugene Clifton at the Memorial Sloan-Kettering Institute in the early fifties.

At that time we studied, on fibrin plate methods, using the Astrup technique, the fibrinolytic activity of tumor tissue, and found that certain malignancies had low fibrinolytic activation, and others had high. I agree fully with the authors that normal tissue like this fibrin plate when plasminogen is placed on them. We found that primary epidermoid carcinomas, had a high inhibitory activity, while primary cancers of the breast and colon had a medium activation and low inhibitory effect, while in our studies smooth muscle tumors, such as leiomyoma and, particularly, leiomyosarcoma, had very high activation of plasminogen and a very low inhibitory activity.

Now, as we all know, the liver was long thought to be the site of antiplasmin or inhibitory production and certainly patients with cirrhosis of the liver were well known to have low inhibitor levels and high fibrolytic activity. Actually, at St. Vincent's Hospital, where we have a large number of cirrhotic patients, we found that when a long-term cirrhotic, even though successfully shunted, lost the plasma fibrinolytic activity that patient may well have had a hepatoma develop.

I would like to ask the authors if they have studied any biopsies of liver cirrhotic tissue or if they have had any experience with hepatomas.

DR. R. KENNEDY GILCHRIST (Chicago, Illinois): As a young man working in Dr. Preston Keyes Department of Immunology, I became convinced that tumor growth results in a factor which favors fibrinolysis. The greater the tumor load, the more the fibrin is dissolved.

Now, intravascular tumor emboli cannot grow until they become attached to the edothelium, and anything which will prevent the laying down of fibrin, or will produce the lysis of it, will favor the growth of metastases. Dr. Keyes was working on anaphylactic shock, and he could produce lethal or nonlethal shock at will. There are two factors that bear upon this.

If you have sensitized animals or birds, and you crush muscle, the lethality of the dose will be increased if you crush muscle, compared with when you do not. However, the main factor is the rate of injection of the antigen into the bloodstream. If you take 50 animals, such as rabbits or pigeons, you can pick every other one, or any one you wish, to kill them by shock by the rate of intravenous injection of the same amount of antigen.

Why do they die, or why do they not die? He showed that, if the antigen was labeled with a dye that would stain to show blue with iron, in the animals that died, sections of the most minute blood vessels in the lung or in the brain would reveal a little dot of blue and around it would be a big ring of fibrin. The size of this ring plus the number of rings determined whether or not the animal died.

If you injected this slowly, the same amount of fibrin would be taken out of the bloodstream; however, these emboli would be small and would not result in the death of the animal. In both cases, the animal is essentially defibrogenated.

This is the basis of our common means of desensitizing patients—a small dose, repeated and the fact that almost all of us know that the patient who has had a severe anaphylactic shock cannot be given another one in less than seven to ten days.

This poses two or three questions. First, does trauma at operation, especially as muscle is crushed or bruised, favor tumor growth by a process similar to that produced by anaphylaxis?

Second, is the inability of a lymphocyte to engulf and destroy a bacillus or a tumor cell caused by a similar process, namely, its inability to become attached to the cell membrane, and tissue destruction, either by trauma or inflammation, playing a role here, much as the other?

Third, is it possible that a citrated blood transfusion, with the frequent presence of innumerable minute emboli, favor a destruction of the defense mechanism, possibly because of a similar process of partial defibrinization?

What happens to this fibrin when it is dissolved I do not know.

DR. ALFRED KETCHAM (Miami, Florida): It is most pleasing to again hear that good investigators continue to be interested in attempting to develop a better understanding of the bizarre vagaries associated with metastases formation. One is particularly intrigued with their attempts to do so through studies with the coagulative mechanisms.

Some years ago the Gassics in Philadelphia developed a technique of identifying which of several experimental tumor systems would be most susceptible to anticoagulative attempts at decreasing their incidence of metastastic tumor development. Numerous groups then demonstrated this means of slightly decreasing primary tumor growth, but more dramatically demonstrating that a standardized rate of metastases in 60–90% of animals could be reduced to a 15–30% rate in selected experimental tumor systems. These results in our laboratory came through the utilization of warfarin anticoagulation of tumor-bearing animals. One of our own members, Dr. William Waddell, was one of the clinical pioneers in utilizing anticoagulative modalities in conjunction with chemotherapy. He demonstrated a strongly suggestive trend of improved patient disease remission with this combined modality. This work along with that of Thornes, a departmental surgical chairman from Dublin, as exciting as it may have been, has not captured the investigative interest of many clinicians and certainly not served to generate any funding potential from those who sponsor clinical trials.

We recently reported the results of a preliminary pilot study with patients bearing osteogenic sarcoma. None of these patients had the more favorably behaving parosteal forms of sarcoma. A selected group who had conventional amputative therapy and who in the past would have had a 20% survival underwent anticoagulation with warfarin, seven days before operation, had the anticoagulation continued during the operation and then for up to six months postoperatively. Three of 21 patients who did not undergo anticoagulation and served as controls were alive 5–11 years after the operation. Five of nine of the patients who did undergo anticoagulation were alive at 6–9 years. We postulated that the presumed mechanism of increased survival periods is an inhibition of fibrin deposition around circulating tumor cells, thereby preventing their adherence to capillary endothelium which may be the initiating means of metastasis formation.

This exciting information is not really different from what is now reported with adjuvant chemotherapy, but the morbidity and complication of anticoagulation, when well monitored, are negligible as compared with the usual problems that can be associated with aggressive chemotherapy.

The Mayo group has just reported an increase in patient survival with primary osteogenic sarcoma which ranges from a 20–25% survival rate for patients treated in the 1960's up to a 50% survival rate at three years for patients similarly treated by operation alone during the early 1970's. Such confusion, however, does not minimize the impact of this material and its relation to preliminary anticoagulative studies in humans. I believe there is a wide avenue of exploration open to the investigator who is interested in the anticoagulative, fibrinolytic mechanism of the patient with cancer. The authors suggest this in their closing comments, and I would first off ask how they propose to use their experimentally obtained clinical data in clinical trial. Second, I would ask for their explanation of why secondary tumor metastases demonstrated significant increases in tumor inhibition of fibrinolysis as compared with primary tumors. Furthermore I am intrigued by the fact that tumors with documented metastasis had this activation—inhibition ratio at a rate which was four times greater than tumors without metastasis.

Fellow oncologists, I believe we must further encourage such stimulating studies in the laboratory but more rapidly integrate them into acceptable clinical protocols.

DR. J. M. MALONE (Closing discussion): Dr. Grossi, I was fascinated to hear your comments on cirrhotic liver. We have looked at cirrhotic liver as part of another study, and we found an identical finding to yours. In the cirrhotic liver, compared with the noncirrhotic liver, there are increased levels of activation and decreased levels of inhibition of fibrinolysis.

We tested several hepatomas. One specimen was from a trisegmentectomy liver resection without metastases (primary tumor without metastases) and the activation/inhibition ratio was less than ten. The other hepatoma was metastatic (primary tumor with metastases) and the activation/inhibition ratio was greater than ten. Both hepatomas demonstrated increased activator and increased inhibitor compared with normal liver.

(slide) Not included in the presentation, but in the text of the paper, are some preliminary comments on what happens to liver with tumor metastasis. Normal liver has a small level of fibrinolytic activator activity, and a low level of fibrinolytic inhibitory activity, and an activation/inhibition ratio less than one. In normal liver in patients with extrahepatic abdominal tumor, hepatic activation is lost and there is a substantial increase in hepatic inhibition of fibrinolysis. In normal liver with intrahepatic tumor (histologically normal liver from a section not involved with tumor) there is a dramatic increase in both activation and inhibition of fibrinolysis.

I do not know what these hepatic changes mean. I hope these changes are going to provide us with a tumor marker that we can use to follow patients who have undergone tumor resection.

Dr. Gilchrist, your comments are very interesting, and I think perhaps the best way to answer them would be to give you my teleologic overview of what I think our data mean. I think that fibrinolytic activator activity may be related to loss of intracellular adhesiveness and, therefore, tumor cell shedding from the primary tumor. I think that the inhibitory activity or the tumor cell is related to the ability of the tumor cell to stick and plant itself on vascular endothelium.

There is no question that trauma such as surgical procedure will increase the fibrinolytic activity of blood. Whether or not surgery itself changes the tumor values, I don't know. Based upon our assay techniques, I can tell you that an operation itself does not change normal endothelial fibrinolytic activator or inhibitory values.

With respect to lymphocytes and tumor cell recognition, there is a lot of work to suggest that lymphocytes may not recognize tumor cells because of circumferential fibrin coats, and it is possible that if you can unmask the fibrin coats on the lymphocytes, that the lymphocytes, in conjunction with macrophages, may then be able to recognize and appropriately kill tumor cells. We are currently doing lymphocyte culture studies to evaluate the role of fibrinolytic agents with respect to lymphocyte antibody production and/or lymphocyte recognition of tumor cells.

Dr. Ketcham, I am familiar with your work and excited that you see some promise in our work. In addition to the results you have published and those of Dr. Waddell, Dr. Thornes in England has similar results of which I am sure you are aware. Utilizing streptokinase as an adjunct for patients with cancer of the colon. Dr. Thornes has demonstrated prolonged patient survival at both two and five years postoperatively.

With respect to whether we will do a clinical trial, the answer is yes. However, as we get closer to the starting date, I am becoming somewhat more conservative and, before starting the clinical trial, I would like to reproduce our results in a known animal tumor model.

I do not know why there is a difference in tumor activation/inhibition ratios. This concept is obviously not a new idea, as all of you are aware. We happened to find a new assay technique by accident. Our assay measurements give quantitative values which have statistically significant differences, but I cannot explain what the data mean. I merely present the data, which I think are fascinating, and suggest that the potential is enormous, and it is worth reanalyzing this area of tumor research.

Enhanced Survival of Patients with Colon and Rectal Cancer is Based Upon Wide Anatomic Resection

WARREN E. ENKER, M.D., F.A.C.S., URBAN TH. LAFFER, M.D., GEORGE E. BLOCK, M.D., F.A.C.S.

From 1966 through 1970 we performed resections in 216 patients with carcinoma of the large bowel. The relative five year survival for all patients was 65.5%. The relative five year survival for all potentially curable patients was 80.4%. Patients with positive lymph nodes and full-thickness penetration of their tumors had a five year survival of 70.5% and a 10 year survival of 60.5%. In performing this study we have tested the principles of wide anatomical resection and radical lymphadenectomy. For their specific influences on survival we have also examined stage, site, age, sex, race, margins, local recurrence, hypogastric lymph node dissection, serosal penetration and various aspects of nodal status. The information derived from these parameters has confirmed our hypothesis that survival is directly related to radical anatomical resection and lymphadenectomy. For rectal cancer, extensive resection also reduces the incidence of local recurrence. We are persuaded that the principles of operation for large-bowel cancer are valid and that they merit universal adoption.

From the Department of Surgery,
The University of Chicago,
Pritzker School of Medicine,
Chicago, Illinois

THE CURE of colon and rectal cancer, more than any other malignant tumor, is a singularly surgical endeavor. The major principles of the curative operations for large-bowel cancer have been established for nearly three-quarters of a century. These include the en bloc resection of lymph nodes to the origin of the named arteries supplying the colon and rectum according to Jamieson and Dobson[10] and Rouviere,[14] as is typified by high ligation of the inferior mesenteric artery for left-sided cancers, resection of the zone of upward spread in rectal cancers according to Miles[11] and wide pelvic and hypogastric lymph node dissection as practiced by Stearns and Deddish.[16]

Wide anatomical lymphadenectomy has been practiced at the various parent institutions with success. Two dilemmas remain: To our knowledge few institutions have consistently applied *all* of these principles to their surgical practice, and, more importantly, the concept of radical lymphadenectomy has not received universal application outside major surgical centers. We are convinced that this latter factor alone is responsible for an unwarranted national pessimism concerning the survival of patients with colorectal cancer.

Since the cure of colorectal cancer is almost exclusively surgical, we have chosen to examine the results of our own operative experience in which we have strictly adhered to all of the above principles. This study was undertaken to test these standards of surgical treatment.

Materials and Methods

From 1966 to 1970, 216 consecutive patients underwent a definitive laparotomy at the University of Chicago Hospitals and Clinics for the treatment of adenocarcinoma of the large bowel. Complete medical records were available for 186 patients (86.1%). Data for the remaining patients were obtained from operative records, surgical pathology reports and attending surgeons' records. All patients (100%) were followed until death or to the present time by the University of Chicago Registry for Neoplastic Diseases.

There were 118 males (54.6%) and 98 females (45.4%). One hundred thirty-four patients were white (62.0%), and 83 patients were black (38%). The mean age of our patients was 63.5 years, with 81% between 50 and 80 years of age and 30% over 70 years of age.

Pathological staging was performed according to the modified Dukes' classification of Astler and Coller[2] (Table 1). Further subsets of our data were analyzed by the modified Dukes' classification of the Gastrointestinal Tumor Study Group of the National Cancer Institute when deemed appropriate[9] (Table 2). Of the 216 patients, four were classified as Stage A (1.9%), 34 patients as Stage B_1 (15.7%), 68 patients as Stage B_2 (31.5%), three patients as Stage C_1 (1.4%), and 62 pa-

---

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

Reprint requests: W. E. Enker, M.D., Box #168, 950 E. 59th Street, Chicago, Illinois 60637.

This study was supported in part by Contract #PHS N01-CM-67095.

0003-4932/79/0900/0350 $01.05 © J. B. Lippincott Company

TABLE 1. *Modified Dukes' Classification of Astler and Coller (1954)*

Stage	Definition
A	Limited to mucosa
B_1	Invasion of muscularis mucosa, submucosa or muscularis propria
B_2	Complete penetration of muscularis propria
C_1	Invasion of muscularis mucosa; lymph nodes involved
C_2	Complete penetration of muscularis propria; lymph nodes involved

TABLE 3. *Distribution of Patients by Stage (Modified Dukes' Classification of Astler and Coller)**

Stage	Number	Per Cent
A	4	1.9
B_1	34	15.7
B_2	68	31.5
C_1	3	1.4
C_2	62	28.7
D	45	20.8
	216	100.0

* 61.6% B_2, C_1 or C_2.

tients as Stage C_2 (28.7%). Forty-five patients (20.8%) were Stage D on accession to treatment. Thus, 61.6% of our patients had advanced but potentially curable primary tumors (Table 3). Patient distribution by pathological stage was essentially unchanged from either the original Astler-Coller series or from our earlier study on the survival of aged patients, indicating no apparent bias in our patient selection[3] (Table 4).

The distribution of patients by the site of their primary tumors revealed that 31 (14.4%) had tumors of the cecum, ten (4.6%) of the ascending colon, 14 (6.5%) of the heptaic flexure, 16 (7.4%) of the transverse colon, 18 (8.3%) of the splenic flexure, 11 (5.1%) of the descending colon, 46 (21.3%) of the sigmoid, 22 (10.2%) of the rectosigmoid and 48 (22.2%) of the rectum (Table 5).

Cancer of the rectum was defined as any tumor of which the lowest edge was within 12 cm of the anal verge on preoperative proctoscopy in Depage's position. By this definition, 48 patients (22.2%) had cancer of the rectum, while 168 patients (77.8%) had tumors of the intra-abdominal colon.

Data was also obtained regarding the distance of the proximal and distal resected margins from the primary tumor (fresh specimen as measured by the pathologist), the gross architecture of the tumor, tumor size, histologic degree of differentiation, number of nodes examined per specimen, number of positive nodes and nodal ratios. All specimens were examined and the staging supervised by one surgical pathologist (Dr. Charles E. Platz) during the period of this study.

Statistical evaluation was performed using the Cox regression model.[5] Five year and ten year survivals were examined as absolute survival (taking into account all causes of death in the cohort), relative survival (death due to cancer only) and survival by life table analysis. Statistical significance at the 5% confidence level was established when the coefficient β was equal to or greater than twice the standard error for any given variable.

Method of Operation

Our operative methods and principles of radical lymphadenectomy have been previously presented in detail.[8] Two items merit special comment. First, sigmoid cancers are generally treated by wide sigmoid resection based on the origin of the inferior mesenteric artery. In addition, both the left common iliac and the aortic-caval bifurcation lymph nodes are frequently dissected with the specimen. Secondly, adjacent organs, *i.e.*, bladder, posterior vaginal wall, prostate or other intra-abdominal and retroperitoneal organs are included in the resection wherever contiguous spread or adherence are evident.

Results

Survival

Fourteen of the 216 patients (6.4%) died within 60 days of operation. The absolute five year survival for all stages of disease (Stages A through D), including those patients with rectal cancer, was 52.8%. The absolute five year survival for all patients without distant metastases (Stages A through C_2) was 65.3%. The relative

TABLE 2. *Modified Dukes' Classification of the Gastrointestinal Tumor Study Group*

Stage	Definition
A	Limited to mucosa
B_1	Invasion of muscularis mucosa, submucosa or muscularis propria
B_2	Invasion of serosa
C_1	One to four lymph nodes involved by tumor
C_2	Five or more lymph nodes involved by tumor
D	Distant metastases

TABLE 4. *Per Cent Distribution of Patients by Stage from 1954–1979*

Modified Dukes' Stage	1954 Astler-Coller	1971 Block/Enker	1979 Enker et al.	Including Stage D
A	0.3	5.0	2.3	1.9
B_1	13.6	18.3	19.9	15.7
B_2	46.6	43.3	39.8	31.1
C_1	4.0	3.4	1.8	1.4
C_2	35.0	30.0	36.3	28.7
D				20.8

TABLE 5. *Distribution of Patients by Site of Primary Tumor*

Site	Number	Per Cent
Cecum	31	14.4
Ascending colon	10	4.6
Hepatic flexure	14	6.5
Transverse colon	16	7.4
Splenic flexure	18	8.3
Descending colon	11	5.1
Sigmoid colon	46	21.3
Rectosigmoid	22	10.2
Rectum	48	22.2
	216	100.0

five year survival for patients with all stages of disease (Stages A through D) was 65.5%. The relative five year survival for patients without distant metastases (Stages A through C_2) was 80.4%. Life table analysis confirmed the high survival by stage observed in the relative survival of patients without distant metastases (Table 6).

While survival was excellent for all stages of curable disease, the rate of death was revealing. Unlike other reported studies, the slope of the survival curves in each group was gradual without precipitous decline in the first two years, suggesting a gradual recurrence of tumor following adequate resection (Fig. 1).

Patients with full-thickness penetration of the bowel wall and involvement of lymph nodes (Dukes' C_2) experienced a 70.5% relative five year survival. At ten years the relative survival for Stage C_2 was 60.7%, indicating that these patients continued to be at risk well beyond the traditional five year period.

The site of the primary tumor had a significant influence on survival. As in other series, patients with rectal cancer did not fare as well as those with intra-abdominal neoplasms. There were no Stage A patients with rectal cancer. Of the 48 patients with rectal cancer, 14 had distant metastases and only one of these patients survived five years. The total survival at five years for all patients with rectal cancer, regardless of stage, was 45.5% (20 to 44 patients). Of the 34 potentially curable patients, four died after operation and 19 of the remaining 30 survived five years (relative survival 63.3%). There was no appreciable difference in the survival of our patients with rectal cancer whether the patients were designated as having a rectal cancer by proctoscopic height or by their tumor's extraperitoneal location as determined at laparotomy (Table 7). Our nine patients with cancer of the ascending colon fared poorly. The relative five year survival for this group was 55.6% (five of the nine patients).

TABLE 6. *Per Cent 5-Year Survival by Stage of Disease*

Modified Dukes' Stage	Absolute Survival	Relative Survival	Life Table Analysis
A	100.0	100.0	100.0
B_1	73.5	87.5	87.0
B_2	64.7	84.7	82.5
C_1	66.7	100.0	100.0
C_2	56.5	70.5	67.4
D	4.4	11.4	6.5

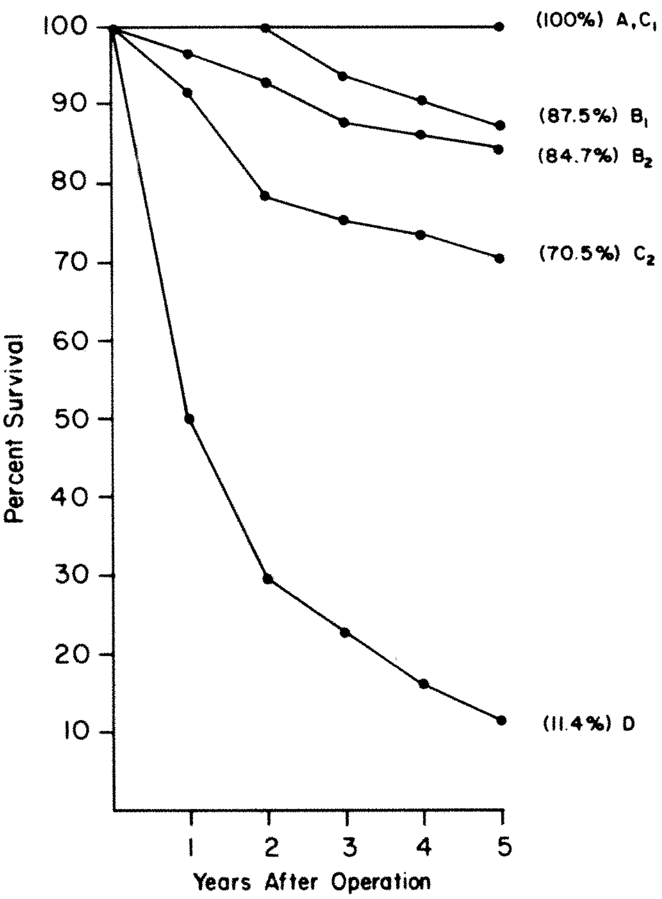


FIG. 1. The relative survival for all patients is graphically displayed. Note that with the exception of patients with widespread metastatic disease (Stage D) the decline in survival is gradual in all groups, without precipitous decline in the first 2 years.

TABLE 7. *Per Cent 5-Year Survival of Patients with Rectal Cancer*

	Defined by			
	Proctoscopic Height Less than 12 cm		Extraperitoneal Location at Operation	
Dukes' Stage	No.	Per Cent Survival	No.	Per Cent Survival
A	0		0	
B_1	10	87.5	15	76.9
B_2	10	62.5	17	64.3
C_2	0		0	
C_2	14	50.0	21	55.0
D	14	7.1	17	11.8

TABLE 8. *Per Cent Incidence of Local Recurrence by Stage (All Sites) and by Distal Resected Margin (Length in Centimeters).*

Dukes' Stage	Length of Distal Margin	Local Recurrence Rate (%) No.	Per Cent
B_1 or B_2	≤5 cm	6/30	20.0
	>5 cm	5/72	6.9
C_1 or C_2	≤10 cm	14/38	36.8
	>10 cm	2/27	7.4

Areas of Known Surgical Failure

We next turned our attention to the areas of surgical failure in order to substantiate our hypothesis that wide anatomical resection and lymphadenectomy are the key elements in the control of this disease. Aside from examining survival as the absolute measure of success, we have also analyzed the following parameters for their influence on the outcome of treatment; stage, local recurrence, distal margins, hypogastric lymph node dissection in rectal cancers, number of lymph nodes involved by cancer, total number of nodes in the resected specimens, nodal ratios and serosal penetration.

Local Recurrence vs. Margins and Stage

While the local recurrence rate at any site of disease was directly related to stage, it was also related to the length of the distal resected margin. In patients with Stages B_1 or B_2 carcinoma, a distal margin of greater than 5 cm was associated with a 6.9% rate of local recurrence. A margin of less than 5 cm resulted in a local recurrence of 20%. For patients with C_2 tumors, in which the three-dimensional extent of local disease was obviously great, a wide anatomical resection with greater margins in all planes was necessary to encompass the tumor. Thus, a distal margin of 10 cm or greater was necessary in order to maintain a rate of local recurrence equal to that seen in patients with Stage B_1 or B_2 disease. Margins of 10 cm or less were associated with a 36.8% rate of local recurrence (Table 8). The rate of local recurrences, stage by stage, was clearly related to the extent of the resection even when judged by the length of the distal margin alone.

Local Recurrence in Tumors of the Rectum and Rectosigmoid

The local recurrence rate for tumors of the rectum and rectosigmoid, including those instances observed after five years, bore a direct relationship to the stage of disease at the time of operation. The local recurrence rate for Stage B_1 was 9.4% and for Stage B_2, 11.9%. Patients with Stage C_2 disease of the rectum and rectosigmoid experienced a local recurrence rate of 27.9% (Table 9).

TABLE 9. *Incidence of Local Pelvic Recurrence in Rectal and Rectosigmoid Cancer by Stage*

Dukes' Stage	Local Recurrence Rate (%)
B_1	9.4
B_2	11.9
C_2	27.9

Hypogastric Lymph Node Dissection

The influence of wide lateral pelvic dissection on the rate of local recurrence in rectal cancer was also examined. While the number of our patients with full-thickness tumors and involved nodes is small, it is reasonable to examine the results of their treatment. Of the 14 patients with C_2 rectal cancers, five (35.7%) developed a local recurrence after resection. All of the three patients who did not undergo a concomitant hypogastric node dissection developed a local recurrence (100%), while only two of the 11 patients in whom a hypogastric lymph node dissection was performed developed a local recurrence (18.2%) (Table 10). As relates to the resection of rectal cancer, the rate of local recurrence in patients with extensive carcinoma of the rectum (Dukes' C_2) was kept to a minimum by extending the plane of dissection to the lateral muscular boundaries of the pelvic wall.

Extent of Resection as Determined by the Pathologists' Criteria

A further judgment concerning the extent of any given resection was based upon the total number of nodes retrieved from the resected specimen. The examination of all specimens consistently by one pathologist has enabled us to generalize on the basis of this data, albeit subjectively. There were 65 patients in Stages C_1 and C_2, *i.e.*, with nodal involvement. The patients were divided into those with ten or fewer nodes found in the resected specimen and those with greater than ten nodes. The mean survival for patients with one to ten nodes in the specimen was 53.2 months, with 45%

TABLE 10. *The Influence of Hypogastric Node Dissection on the Local Recurrence Rate in Patients with C_2 Rectal Cancers*

Hypogastric Lymph Node Dissection	No.	Local Recurrences
Performed	11	2 (18.2%)
Not performed	3	3 (100%)
	14	5 (35.7%)

TABLE 11. *Comparison of Low Anterior Resection vs. Abdominoperineal Resection in the Treatment of Rectal Carcinoma*

	Low Anterior Resection (N = 11)	Abdominoperineal Resection (N = 33)
Stages B_1 or B_2	36.4%	45.5%
Stages C_1 or C_2	63.6%	54.5%
Relative 5-year survival (all stages)	52.4%	41.4%
Relative 5-year survival (Stages B_1–C_2)	87.5%	63.6%
Local recurrence rate	12.5%	24.0%

of the patients dying from metastatic cancer. By contrast, patients with more than ten nodes in the specimen had a mean survival of 71.2 months, and only 26.7% of these patients died from metastatic cancer.

Thus, an examination of surgical failures and the influence of margins, wide pelvic dissection and radical mesenteric resection confirms our hypothesis that wide anatomical resection and lymphadenectomy result in enhanced survival, a decreased incidence of local recurrence and fewer deaths due to cancer.

The Operative Management of Rectal Cancer

The influence of the type of operation upon survival was examined in patients with rectal cancer. Of the 48 patients with rectal cancer, three were treated with limited or partial proctectomy (less than 20 cm total specimen length) for palliation. All died as a consequence of their disease soon after recovering from operation. One patient with a B_1 carcinoma arising in chronic ulcerative colitis was treated by total proctocolectomy with the proctectomy performed in a radical fashion. This patient is alive and well more than 100 months following operation. Of the remaining patients, 33 (68.0%) underwent an abdominoperineal resection, and 11 (22.9%) a low anterior resection. For the patients undergoing abdominoperineal resection, the operative mortality was 12.1%, but no deaths occurred in the patients undergoing low anterior resection. Many of these deaths were related to hemorrhage, perineal sepsis or to the need for reoperation (28.6%). The majority of patients undergoing abdominoperineal resection had less advanced tumors when compared to those in the low anterior resection group (45.5% vs. 36.4% Stage B tumors and 54.5% vs. 63.7% Stage C or D tumors, respectively). The five year survival in patients undergoing low anterior resection was nearly 20% better than that observed in patients undergoing abdominoperineal resection, despite the apparent advantage by stage in the latter group (Table 11). From this data it is apparent that, when properly selected, the low anterior resection is a worthwhile procedure which does not *per se* compromise survival. The decision to perform a low anterior resection remains an intraoperative one and is based upon the ability to accomplish a wide pelvic dissection with a 5 cm margin while preserving a distal segment of rectum sufficient to accommodate an anastomosis. This intraoperative selection of appropriate tumors may account for the apparently enhanced survival following low anterior resections.[6]

Alternative Factors in Staging and Prognosis

The prognostic importance of positive lymph nodes and muscular penetration of the bowel wall are acknowledged. However, the modified Dukes' classification of Astler and Coller does not take into account the prognostic significance of either the number of involved lymph nodes or the presence or absence of serosal extension. It is apparent, nevertheless, that patients with only one or two involved nodes and those without complete transmural penetration have a considerably better course than patients with extensive nodal involvement or pericolic invasion. For this reason we have re-examined subsets of our data according to the modified Dukes' classification of the Gastrointestinal Tumor Study Group in which these two factors are taken into account.[9]

The 65 patients with positive lymph nodes (Stages C_1 and C_2) but without distant metastases were divided into Stages C_1 and C_2 of the Gastrointestinal Tumor Study Group Dukes' classification. Stage C_1 represents patients with one to four positive lymph nodes, while Stage C_2 includes patients with five or more positive nodes divorced from any consideration of penetration by the primary tumor. The 51 patients with C_1 disease had a mean survival of 73.4 months, and 27.5% of these patients died from recurrent cancer. In contrast, those with five or more positive nodes (C_2) had a mean survival of only 58.9 months, with 50% dying of metastatic disease. When the patients were divided by the presence or absence of serosal involvement, the relative five year survival rate was appreciably less for patients with serosal extension. In patients without lymph node involvement the difference in survival was 12.1%, and for patients with lymph node involvement there was a 22.3% inferior survival in those patients with serosal extension (Table 12). These data confirm the value of the Gastrointestinal Tumor Study Group's staging method as a refinement of the original Astler and Coller Dukes' classification for determining prognosis.

Lymph node ratios (positive/total) were of little prognostic significance, with no clear pattern of death or survival until 70% or more of the examined lymph nodes were found to contain tumor (Fig. 2).

Additional Parameters Affecting Survival

As expected, the five year survival for women (70.7%) was slightly better than that for men (65.0%). However, contrary to prevailing opinion, the five year survival for black patients (74.4%) exceeded that of white patients (63.4%). There was a 20% increase in the death rate per decade of age above the mean of 63.5 years. Patients with well-differentiated tumors experienced a five year survival of 69.7%, while those with poorly differentiated tumors had a 50.0% five year survival. The presence of an exophytic or polypoid cancer was associated with a five year survival of 76.8%, while the patient with infiltrative or sessile cancers had a five year survival of 63.3%.

Obstructing colon cancers had a poorer prognosis. Patients without radiologic evidence of obstruction had a five year survival of 72.0%, while those with obstruction had a five year survival of only 54.2%. There was no difference in the operative mortality of the groups with or without radiographic evidence of obstruction. Only four patients with perforating tumors were treated during this period.

Statistically significant differences in survival were attributable to age, site (rectum and ascending colon) and Stage D disease, while pericolic extension approached a significance level of p = .08.

Operative Complications and Deaths

There were 25 intraoperative complications of significance in our 216 patients. Six of these 25 patients died as a direct result of an intraoperative complication. The majority of these deaths were associated with either excessive bleeding or contamination. While there were nine instances of visceral injury recognized by the operating surgeon, only one patient, who had an injury to the left ureter, ultimately died as a consequence of a recognized injury to an adjacent structure (Table 13).

Fourteen patients (6.4%) died within 60 days of operation. There were 21 recognizable complications contributing to death. Fifteen of these were related to operative or management errors. Five patients died as a consequence of bleeding, and three patients (1.6%) died as a consequence of anastomotic leaks. Six of the 21 complications were not directly related to operative technique, four of these were myocardial infarction (Table 14). Utilizing the same techniques and principles of operative management, our operative mortality has been 1.9% during the past three years.

TABLE 12. *Influence of Serosal Penetration or Pericolic Invasion on Survival*

Stage	Serosal Penetration	No. Patients	Per Cent Relative Five-Year Survival		Per Cent Absolute Five-Year Survival
B_2	Absent	27	74.1		90.9
	Present	41	63.4		78.8
				Difference	12.1%
C_2	Absent	16	62.5		83.3
	Present	46	54.3		61.0
				Difference	22.3%*

* $\beta = .7686 \pm .4378$, p = .08.

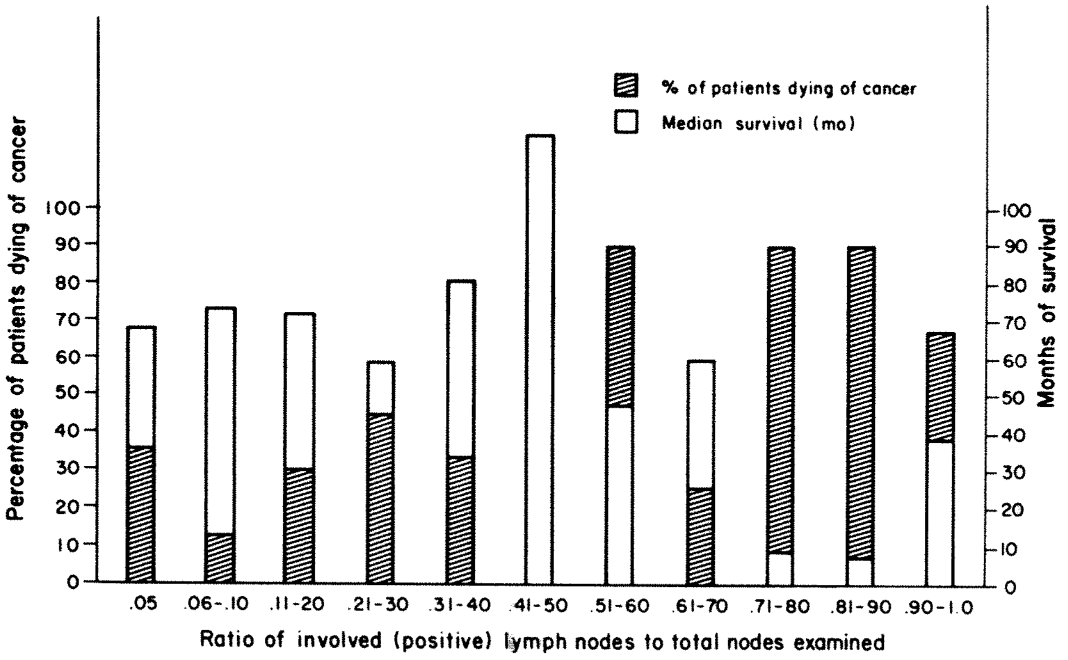


FIG. 2. The influence of nodal ratios on prognosis. Median survival in months and the per cent of patients dying from cancer are plotted for the various ratios of positive lymph nodes to total nodes examined. There is no consistent pattern of survival or death until a ratio of .71 or greater is achieved.

TABLE 13. *Intraoperative Complications*

Complication	No.	Related Deaths
Bleeding (>2 liters)	5	2
Contamination	11	3
Visceral injury	9	1
Spleen	2	
Bladder	2	
Intestine	2	
Ureter	1	(1)
Liver	1	
Pancreas	1	
Total	25	6 (24.0%)

Discussion

The data in this consecutive series confirm and underscore the value of the established principles for operating on large bowel cancer. By the method described above, we have been able to offer a relative five year survival, which is tantamount to cure, to 80.4% of all patients with colon cancer and to 63.3% of the patients with rectal cancer who do not have distant peritoneal seeding or liver involvement at the time of operation. This is true despite the fact that 61.6% of these patients had advanced but potentially curable primary tumors, while 38.4% of these patients had tumors limited to "all coats" of the bowel wall.

When we compare these survival figures with other published data it is clear that the prevailing national pessimism concerning survival from colorectal cancer is unwarranted. In a recent study by the American Cancer Society, it was demonstrated that the national and Illinois survival figures are extremely comparable, if not virtually interchangeable. The National Cancer Institute End Results Data for 1965–1969, covering 9681 patients, indicate a relative five year survival of 43% for males and 46% for females.[7] The American Cancer Society statistics for 1968–1970 concerning the survival of 2555 patients treated at 32 hospitals indicated a relative five year survival of 45.6% for males and 48.1% for females.[1] Forty-six per cent of the patients in both series were males and 29% of the American Cancer Society's Illinois patients were designated Stage III (regional spread and/or involvement of regional lymph nodes). Only 11% were black, while 88% were white. In the present series 54.6% of our patients were male, and 38% were black, both of which factors are reported to negatively influence survival. Despite these less advantageous features, our own relative five year survival for all stages was 65.5% and 80.4% for patients with colorectal cancer in Stages A through C_2.

Furthermore in examining the survival by stage the five year survival of patients with Stage III took on even greater significance. In this group, which represents the greatest challenge to the surgeon, the five year survival in institutions reporting ten or more patients varied from 10.3–45.5% (the latter figure covering only 11 patients). In the same report the observed five year survival of the 45 patients operated upon at our own institution was 66.6%. Thus, despite several negative prognostic features in our own patient population we have achieved a cure rate which is two to three times the local and national averages. We attribute this achievement to our strict adherence to the prescribed principles for operating on this disease. During the course of this study we did not systematically employ either chemotherapy or irradiation, except in patients with metastatic or recurrent disease.

Other institutions which have similarly persisted in their efforts to treat colon and rectal cancer according to these same principles have reported equally dramatic cure rates.[15] These reports strengthen our hypothesis and serve to reinforce our belief that the adoption of radical anatomic resection and lymphadenectomy as practiced at the various major centers would improve the national success rate.

These operative principles have been known to surgeons for nearly 75 years. Thirty years prior to the classic contribution of Rouviere,[14] the lymphatic-arterial supply of the colon and its surgical implications were exquisitely described by Jamieson and Dobson.[10] In the year 1908, Moynihan described the logic of and his experience with ligation of the inferior mesenteric artery at its origin for patients with cancers of the descending and sigmoid colon.[12] He emphasized that the only element standing in the way of a radical resection based upon ligation of the inferior mesenteric artery at its origin was the willingness of the surgeon to perform adequate mobilization of the splenic flexure for suitable reconstruction. When these works are viewed in combination with the honored contributions of Miles, it is apparent that the entire foundation for adequate resection of large bowel cancer was established by the year 1908.[11] While Moynihan translated the principles of high ligation into practice, it

TABLE 14. *Postoperative Complications Contributing to Operative Mortality*

All deaths		14 (6.4%)
Major complications		21 (9.7%)
Related to operative or postoperative management		15
Bleeding	5	
Anastomotic leak	3	
Sepsis (undefined)	3	
Mechanical ileus	2	
Wound infection	1	
Aspiration pneumonia	1	
Related to operative risk		6
Myocardial infarction	4	
Cardiovascular accident	1	
Pneumonia	1	

was Rosi who provided an objective rationale for its use. Rosi et al. demonstrated that anywhere from 8–22% of patients with sigmoid carcinomas had lymph node metastases within 1–3 cm from the origin of the inferior mesenteric artery and that survival was directly affected by the level or arcade at which the mesentery was divided.[13] The role of the hypogastric lymph node dissection (in the unirradiated patient) and the prevention of intraoperative spread of disease followed later.[16] Cole et al.[4], and subsequently Turnbull et al.[17], were concerned with the possibility of spread of tumor by intraoperative manipulation, based upon the experimental work of Tyzzer.[18]

Turnbull et al. recently popularized the principles of radical colon resection. However, we are not persuaded that the success of his operative endeavors lies in the stepwise execution of his "no touch technique."[17] Rather, the anatomical scope of the resection, which is implicit in his method, results in a radical anatomic lymphadenectomy. In the present series no special attention was devoted to executing the "no touch" guidelines in any particular order. Despite this, our results in terms of survival exceed those of the Turnbull series on the "no touch technique." In the two comparable groups, Turnbull's Stage C patients and our Stage C_2 patients, the life table five year survivals were 57.8% and 67.4%, respectively. We are therefore persuaded that it is the anatomy and extent of the resection which is operative in cure, not so much its order of execution.

In the case of rectal cancer, the principles of adequate resection are the key determinants not only in regard to survival but also in reducing the rate of local recurrence. While the number of patients in this series is too small to judge any one factor in isolation, the combination of the data regarding stage, margins, hypogastric lymph node dissection and the number of nodes per specimen leads to the conclusion that the cure of rectal cancer is equated with radical pelvic and mesenteric lymphadenectomy. Since it is not our practice to routinely employ preoperative radiation in patients with rectal cancer, we have only infrequently encountered some of the difficulties inherent in hypogastric lymph node dissection that have been experienced in irradiated patients.

In 1908, Moynihan closed his paper on colorectal cancer with the statement "operations which merely go 'wide of the disease' do not meet the necessities of the case. We have not yet sufficiently realised that the surgery of malignant disease is not the surgery of organs: it is the anatomy of the lymphatic system."[12]

The same message is even clearer today after having borne the test of time. If the principles of radical curative resection of large bowel cancer were to be translated into common use, the national cure rate of this disease would rise and the prevailing pessimism would decline accordingly. We are persuaded that this study has served to emphasize the value of these principles.

Acknowledgments

Dr. Charles E. Platz, University of Iowa was responsible for the painstaking evaluation of the pathologic specimens examined between 1966 through 1970. Data retrieval was conducted with the assistance of Mrs. Florence Lowenstein and the University of Chicago, Registry of Neoplastic Diseases. Mr. Theodore Karrison was responsible for all the independent statistical evaluations. We wish to thank Mrs. Lorraine G. Williams for her assistance in the preparation of this manuscript.

References

1. American Cancer Society: Results in Treating Cancer. Colon Cancer, Report No. 2. Chicago, American Cancer Society, Illinois Division, 1977.
2. Astler, V. B. and Coller, F. A.: The Prognostic Significance of Direct Extension of Carcinoma of the Colon and Rectum. Ann. Surg., 139:846–852, 1954.
3. Block, G. E. and Enker, W. E.: Survival After Operations for Rectal Cancer in Patients Over 70 Years of Age. Ann. Surg., 174:521, 1971.
4. Cole, W. H., Packard, D. and Southwick, H. S.: Carcinoma of the Colon with Special Reference to Prevention of Recurrence. JAMA, 155:1549–1553, 1954.
5. Cox, D. R.: Regression Models and Life Tables. J. R. Stat. Soc. B., 34:187–220, 1972.
6. Deddish, M. R. and Stearns, M. W., Jr.: Anterior Resection for Carcinoma of the Rectum and Rectosigmoid Area. Ann. Surg., 154:961, 1961.
7. End Results in Cancer, Report No. 4. Bethesda, Md., Department of Health Education and Welfare, U.S. Public Health Service, National Institutes of Health, pp. 51–68, 1972.
8. Enker, W. E.: Surgical Treatment of Large Bowel Cancer. *in* Enker, W. E. (ed): Carcinoma of the Colon and Rectum. Chicago, Yearbook Medical Publishers, pp. 73–106, 1978.
9. Holyoke, E. D., Lokich, J. and Wright, H.: Adjuvant Therapy of Adenocarcinoma of the Colon Following Clinically Curative Resection. Bethesda, Md., Proceedings of the Gastrointestinal Tumor Study Group, Division of Cancer Treatment, National Institutes of Health, National Cancer Institute, 1975.
10. Jamieson, J. K. and Dobson, J. F.: The Lymphatics of the Colon: With Special Reference to the Operative Treatment of Cancer of the Colon. Ann. Surg., 50:1077–1090, 1909.
11. Miles, E. E.: A Method of Performing Abdomino-perineal Excision for Carcinoma of the Rectum and of the Terminal Portion of the Pelvic Colon. Lancet, 2:1812–1813, 1908.
12. Moynihan, B. G. A.: The Surgical Treatment of Cancer of the Sigmoid Flexure and Rectum: With Especial Reference to the Principles to Be Observed. Surg. Gynecol. Obstet., 6:463–466, 1908.
13. Rosi, P. A., Cahill, W. J. and Carey, J.: A Ten Year Study of Hemicolectomy in the Treatment of Carcinoma of the Left Half of the Colon. Surg. Gynecol. Obstet., 114:15–24, 1962.
14. Rouviere, H.: Anatomy of the Human Lymphatic System. (Translated by M. J. Tobias) Ann Arbor, Michigan, Edward Brothers, Inc., pp. 188–192, 1938.
15. Stearns, M. W., Jr.: Benign and Malignant Neoplasms of the Colon and Rectum: Diagnosis and Management. Surg. Clin. North Am., 58:605–618, 1978.
16. Stearns, M. W., Jr. and Deddish, M. R.: Five Year Results of Abdomino-pelvic Lymph Node Dissection for Carcinoma of the Rectum. Dis. Colon Rectum, 2:169–172, 1959.
17. Turnbull, R. B., Jr., Kyle, K., Watson, F. R. and Spratt, J.: Cancer of the Colon: The Influence of the "No Touch Isolation" Technic on Survival Rates. Ann. Surg., 166:420–425, 1967.
18. Tyzzer, E. E.: Factors in the Production and Growth of Tumor Metastases. J. Med. Res., 28:30, 1913.

DISCUSSION

PROFESSOR JOHN GOLIGHER (Leeds, England): I should like to comment on the use of superradical surgery for rectal cancer.

I approach this subject in a prejudiced frame of mind. My bias springs from two considerations: partly from my own disappointing experiences in the early 1950's with this sort of operation, with internal iliac adenectomy and partly from the report in 1958 by Stearns and Deddish describing the results of this operation at the Memorial Hospital in New York. They found that it did not enhance the five year survival rate and that virtually all the patients who had metastases in the internal iliac nodes removed subsequently died with pelvic recurrence. In fact, the only effect of the operation seemed to be to increase considerably the immediate postoperative complications, particularly in regard to the bladder and sexual function.

Now comes this enthusiastic reappraisal of this issue by Dr. Enker and his colleagues, with their clarion call to more aggressive surgery. What are we to believe, and what are we to do? Well, with the utmost respect, I have to say that the improvement in results reported by Dr. Enker with internal iliac adenectomy seems so dramatic it immediately arouses my suspicion. For one thing, the number of cases concerned is small, and the differences observed might well be entirely fortuitous. Second, it is not at all clear how patients were selected for dissection or nondissection of these pelvic nodes. Was the decision based entirely on the personal predilection of the surgeon operating, or might it have been due to the heavy involvement of the nodes, making them fixed so that they were, in fact, irremovable? Certainly, we cannot be sure that the two series, with and without internal iliac node dissection respectively, were truly similar. I may add that nothing in my experience of doing many clinical studies of this kind is so important as the absolute comparability of the groups being contrasted.

My feeling is that, if we are ever to get to the truth of this matter, we will have to set up a properly controlled, randomized, prospective trial, but I do not for one moment underestimate the difficulties of so doing, and I think these difficulties may prove insuperable. It will not be easy to get patients to accept two grades of radicality. Of course, it will take at least four or five years in most centers to accumulate a sufficient number of patients to run such a trial of any validity. Then you would have to add another five years for follow-up of all the patients including those most recently brought into the series, so we are talking about a ten year study.

DR. RICHARD E. WILSON (Boston, Massachusetts): We have had the opportunity at the Peter Bent Brigham Hospital to review an 11 year experience with our results of the surgical treatment of colorectal cancer, looking particularly at patterns of recurrence and factors responsible for recurrence.

(slide) We found that 67% of our recurrences, in fact, were either distant or distant plus regional, and only 33% of recurrences—this is for the entire colonic series—were regional only.

(slide) We found that two factors were responsible for recurrence *per se*: that is, the size of the tumor (the smaller tumors were significantly less likely to recur) (slide) and the Duke's-Kirklin stage, where the C_2 patients had the highest incidence of recurrence.

(slide) However, the sites of the primary tumor were, in fact, most determinant of the pattern of recurrence. For all of the colonic lesions except the rectum, distant recurrence or distant plus simultaneous regional recurrence was the major pattern of relapse. In the rectum, regional recurrences and distant recurrences had the same incidence.

One can see that abdominoperineal resection, which was done most frequently in our hospital, was the only type of operative procedure in which the regional recurrence was equivalent to distant and distant plus regional recurrences.

Therefore, it is important to understand that there are many important biologic factors responsible for recurrence. While I believe that the surgical technique must be an important part of the equation, effective systemic therapy will be the most important method of altering the present results in the treatment of this disease. Unfortunately we do not have effective chemotherapy at this time.

DR. JEROME J. DECOSSE (New York, New York): Dr. Enker kindly allowed Dr. Maus Stearns, Chief of our Rectal and Colon Service, and me to review their manuscript. We welcome a reaffirmation of the thesis that more attentive adherence to well-established surgical principles of resection, particularly an adequate margin of mesentery, will reduce recurrence.

It is notable that the American College of Surgeons' Cancer Commission Survey recently reported a five year survival rate for patients with C lesions of 28%. The National Cancer Institute end results have reported a five-year survival rate of 35%. In contrast, the Cleveland Clinic has reported a five year survival rate of 58% for C lesions, Memorial Hospital, 52% and in this paper Enker describes five-year survival rates of 66.7 and 56.5% for C_1 and C_2 cancers, respectively. All advocate aggressive resection.

We do not understand a lower incidence of local recurrence in the pelvis after anterior resection as compared with abdominoperineal resection. Possibly, this reflects the smaller number of anterior resections reported.

I would like to ask Dr. Enker for a clear definition of "local recurrence" with respect to the rectum. With intraperitoneal anastomoses, true local recurrence is extremely infrequent. With extraperitoneal rectal anastomosis, intrapelvic recurrence was present in about one half of the failures, or about 25% of all patients, and this was not influenced by pelvic lymph node dissection, as reported by Stearns and Deddish in 1959.

DR. R. KENNEDY GILCHRIST (Chicago, Illinois): I thought some of you may not have really studied the lymphatic metastasis. I was interested here to see that as many as ten nodes were examined.

(slide) Forty years ago, we modified the Spalteholz method of clearing specimens, and on abdominoperineal resection we averaged 55 different lymph nodes individually sectioned, full-scale drawings, in the abdominoperineal region and almost as many in the right colon: we weren't doing adequate resections on the left colon.

I want to show what happened when these patients died in the hospital after the operation. No patient who had an ordinary postmortem examination who had positive nodes in the specimen had any cancer demonstrated.

Our criteria for operability was any tumor in which we could remove all of the tumor and any other structure it might be adherent to in one piece without breaking into it, no matter where, if we could find no distant tumor that was potentially curable.

Patients who died, and in whom we cleared the retroperitoneal tissues from the celiac axis down, are an example. There is a great difference in the lateral spread between those tumors that are below the peritoneal reflection and those that are above. This patient had many metastases, the large nodes being solid with tumor, the small nodes eclipsed or partial. We noted that if we had gone higher to take off the inferior mesenteric, we would have got that one, but this little one lateral to the foramen ovale would have been missed.

(slide) This patient had many metastases. The tumor is just at the peritoneal reflection. Again, these nodes could have been removed by a radical resection.

(slide) Here is an obstructive resection in a fat, poor risk patient, again, the resection was not quite high enough.

(slide) This last tumor had 47 nodes. One of our well-known groups in New York had performed a biopsy on this tumor the year before and treated it with x-ray irradiation. A year later the patient came in to have the abdominoperineal resection; 47 nodes were involved. The tumor is below the peritoneal reflection, and only one node, laterally, is involved. The postmortem examination of the liver and everywhere else failed to show anything.

(slide) Regarding the cure rate, of the 53 patients who had extraperitoneal lesions, all or part of the tumor being below the peritoneal reflection, 26 with nodes positive, or 49%, were free of disease five years. Actually, two more of those turned up more than ten years later.

Eighty-eight per cent of those who had no nodes involved, the tumors being below the peritoneal reflection at the bottom of the pelvis, were free of disease, whereas 60% of those with tumors just above the peritoneal reflection had positive nodes, and 100% had negative nodes. These figures include all patients who were operated upon, including those who died in the hospital and those who did not and those who were presumed to have died of tumor, though some of them did not.

It has to be recognized that if an operation is done out laterally, as Dr. Goligher says, there may be a lot of trouble.

We had in a definite period 13 women that we operated upon for symptomatic Krukenberg tumors of the ovary, so I also took out the ovaries of the next 102 women upon whom I did resections of the colon when there was an abnormal ovary, when the ovary was near the tumor and when the tumor had broken through the serosa, maybe only to the extent of making these little blisters you see occasionally. There were no ovarian recurrences in those patients whose ovaries were not removed.

I thought this was simply like taking out the omentum; it kept the recurrence from growing rapidly. A good many years later, one of the patients whose ovaries I had removed came in some 12 or 15 years later. After going back over her specimens, I found that she had had a small metastasis in one of these ovaries. In that case this operation was curative, though I really did not consider it such. I agree with Dr. Enker's thesis.

Dr. Owen H. Wangensteen (Minneapolis, Minnesota): Some of you may recall that about 35 years ago, in 1944 and again in 1946, some of my colleagues and I advised near-total or total excision of the large bowel for cancer of the rectum and colon some distance above the sphincter. I rise to mention only lessons we have learned from the near-total colectomy experience.

I had a 31-year-old patient in whom 18 years previously (August 1947) I excised the colon and lower rectum for a low-lying cancer of the midrectum 5 cm above the anus to about 5 cm from the ileocecal valve. He can back every year for 13 years in good shape. Then he did not show up until the eighteenth anniversary of his operation, when he was pale and anemic; it was obvious he had a recurrence. That recurrence was close to the ileocecal valve. So we scrutinized our list of patients who had undergone near-total colectomy, of which there were nine. We sent for all of them. Three of those nine patients also had cancer in the residual portion of the colon. All four who underwent second-look operations are well today.

As Basil Morson of St. Mark's Hospital for Rectal Diseases in London has shown so nicely, contrary to the views of Drs. Castleman of Boston and Spratt and Ackerman of Washington University in St. Louis, there is a real hazard of adenomatous colic lesions becoming malignant. I believe that Basil Morson has succeeded in persuading all pathologists that there is a real hazard of malignancy in adenomatous colic lesions.

Of those four patients, the one who had his lesion resected at 5 cm above the anus and the other three are all alive today. There is obviously a distinct advantage in doing a total over a near-total colectomy.

Dr. Isidore Cohn, Jr. (New Orleans, Louisiana): We cannot compete with the figures shown by Dr. Enker and his colleagues, nor with the use of the English language by Professor Goligher, but, using the Charity Hospital statistics, we can provide numbers that perhaps some of the others do not have.

(slide) The Charity Hospital experience includes more than 2,000 patients, all of whom have been followed a minimum of five years or to death, and all of whom have histologic confirmation of the diagnosis, the level of the lesion, and the involvement of the lymph nodes. It is clear here, as it was in Dr. Enker's presentation, that survival is distinctly better in those patients who had negative nodes, as compared with those who had positive nodes at the time of operation. This is not a new observation, but there are the numbers to confirm it once again.

(slide) The next slide shows the same kind of information based upon the Dukes' classification. Even though our five year survival rate is not as good as in the Chicago series, it is quite clear that the survival rate is better if you have a lesion at the Dukes' A level, as compared with one at the B or the C level.

While it may be true that one should not extend the limits of the operation too far, it is clear that a more extensive operation is better than a highly confined one. I would like to go on record as suggesting that we would do better to extend our operative procedure, rather than to confine it.

Dr. Alfred Ketcham (Miami, Florida): I have seen recently on referral three low rectal lesions which were recurrent after anterior resection.

We were challenged today with a reference to training, teaching and working with our residents, and in this day when some of us know better how to use a stapler than a needle holder, I believe it appropriate to bring those three patients to your attention.

I would encourage us to remain cognizant of the quality of survival of our patients and to try to avoid the colostomy when feasible, but I do believe that we must question the limited en bloc resectability of lesions that are one to two inches within the anus. All three of the patients I saw had low anterior resection with transrectal EEA stapling of the anastomosis. In each of these three patients, I could readily palpate the recurrence by digital examination, two of these patients also had extramural local recurrence.

Dr. Warren E. Enker (Closing discussion): It is obvious to everybody here, as well as myself, that we are indebted to Leeds for a lot more than the history of the lymphatic anatomy, and I greatly appreciate Dr. Goligher's insights, because they are 100% correct. We acknowledge that this is an extremely small group of patients in which to study the benefits or the debits of hypogastric lymph node dissection. We were stimulated to do so, essentially, by Dr. Block's original interest in extending the plane of dissection based on anatomic considerations and the known patterns of lymphatic metastases in patients who may have lateral spread, but who are still potentially curable. We cannot stage colorectal cancer by our fingers and must choose our method of dissection ahead of time.

I must say that in our own patients whom we have examined for hypogastric node dissection, we have not seen an overall increase in survival rate. Those findings which we have examined are essentially the same as those of Stearns and Deddish, in which they found a lower incidence of local recurrence without an effect on survival. We do have patients in whom the pathologic specimen, carefully examined, showed only hypogastric or internal iliac nodes positive. We have anecdotal experience with that, but it is still three or four patients, and they are all alive today because of that dissection.

As far as urinary consequences of this operation are concerned, it is a matter of how you view it. To us, it is just a part of the management of the patient, that the patients who have a hypogastric node dissection may eventually require Urecholine, and anywhere between 10–25% of the men will eventually require a transurethral prostatectomy. Thank you for your comments and your insights.

As far as Dr. Wilson is concerned, I appreciate his comments on local recurrence, and the fact that he has brought it to our attention that this is only part of a spectrum of recurrence in the disease at the time that the disease does recur. I appreciate what he has to say about systemic treatment, but I have to differ with him in the fact that I would only accept the results of systemic treatment once the surgeons of the United States have standardized survival based on an adequate operation.

Dr. deCrosse asked why we have a lower incidence of local recurrence in patients undergoing low anterior resection. This series is too small to answer that question in any controlled or intelligent fashion. However, I suspect that at the time of an operation, depending on various criteria, including the cancer, the male and female pelvis and resectability, there is a certain element of selection of tumors with more favorable characteristics for low anterior resection.

Dr. Gilchrist's name has been associated with the study of this disease for quite some time and I acknowledge the contribution that he has made in this regard. The concept was there since 1908, and gentlemen like Dr. Gilchrist and others have given us a confirmation of the basis for resection.

He brings up a different area, the question of oophorectomy, as was first pointed out by Dr. Quan and associates at Memorial Hospital in New York, and we have practiced oophorectomy. I perform oophorectomy on every female who is undergoing resection for a carcinoma of the colon because of this rationale. More to the point is the question of adjacent organs.

In some staging methods, patients with adjacent organ involvement are placed in a Stage D category, yet Polk and Prohaska, in separate series, have shown that 50% of these patients can be cured despite advancement of their tumors to an adjacent organ. The magnitude of our operations is such that we go around whatever the boundaries of the tumor are to resect adjacent organs in addition to a radical lymphadenectomy.

Dr. Wangensteen, I very much appreciate the fact that you have chosen to discuss this paper, and I think your comments on the spectrum of neoplasia and the biology of this tumor as well as the fact that the entire colon is a potential for neoplasia are important.

We appreciate Dr. Cohn's "charitable" remarks; and, obviously, the single most important factor, once the surgical treatment is standardized, is the relation of stage to prognosis.

To Dr. Ketcham goes the award for raising what is probably the most controversial aspect of this operation. The point that I would like to make about the stapler is this. Its use is probably limited in value to the patient in whom you can get away with retaining rectal function after an adequate or a good cancer operation.

Dr. Goligher spoke to us in Chicago approximately six months ago about the way he uses the stapler. This is a model in many respects for the use of the stapler. Once one has accomplished a dissection of the pelvis in all three planes, and is satisfied that one has not "coned" down to the point of anastomosis to prepare oneself in that regard, and possibly has compromised the extent of the pelvic dissection, if there is sufficient bowel remaining for a staple anastomosis, but one which would be technically impossible for a nonstaple anastomosis, the stapler is of value. But it is the extent of the resection which counts first. It is in this regard that the wide pelvic dissection is ensured by choosing a plane on the boney and muscular boundaries of the pelvic wall. Possibly this is the most important element of dissection which we are learning from hypogastric node dissection—not necessarily the nodal basin itself.

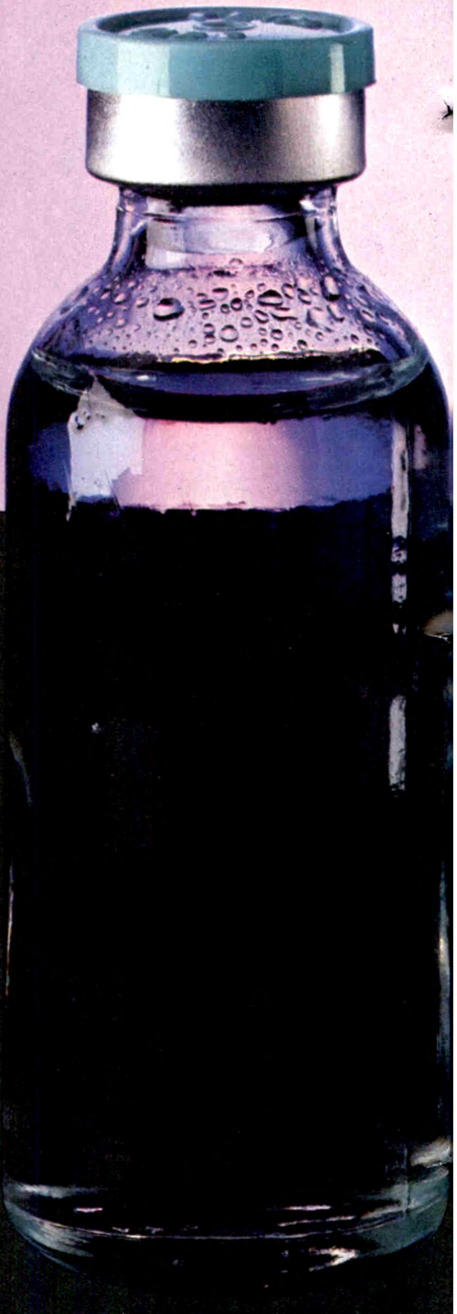
ENDO LABORATORIES TAMES THE POPPY—
TO BRING YOU

new **NUBAIN**®
nalbuphine HCl

new

NUBAIN® AMPULS AND VIAL

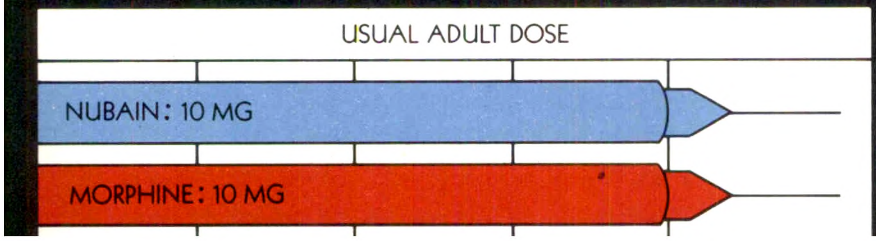
nalbuphine HCl



ANALGESIA COMPARABLE TO MORPHINE

NUBAIN offers:
onset, peak and duration comparable to morphine

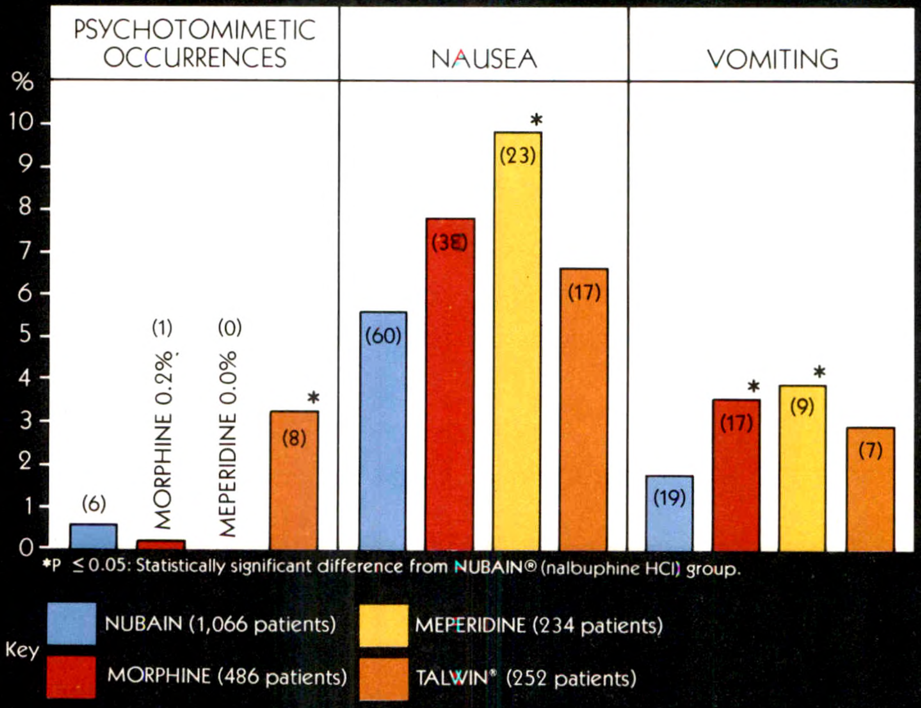
- 10 mg of NUBAIN is comparable in analgesic effect to 10 mg of morphine
- Onset of action with NUBAIN begins within 2 to 3 minutes I.V., and less than 15 minutes I.M. or S.C.
- Analgesic effect of NUBAIN lasts from 3 to 6 hours



WITH A LOW INCIDENCE OF SIDE EFFECTS

Clinical studies show: low incidence of nausea, vomiting and psychotomimetic effects

IN 27 SINGLE OR CROSS-OVER CLINICAL STUDIES (2,038 DRUG EVALUATIONS) THESE SIDE EFFECTS WERE OBSERVED:[1]



*P ≤ 0.05: Statistically significant difference from NUBAIN® (nalbuphine HCl) group.

1. These clinical studies involved patients with pain from a variety of medical causes, including labor, cancer, and orthopedic and general surgical procedures. Actual number of patients experiencing each side effect is shown in parentheses on the bar graphs. Data on file, Endo Laboratories, Inc.

Endo Laboratories DU PONT

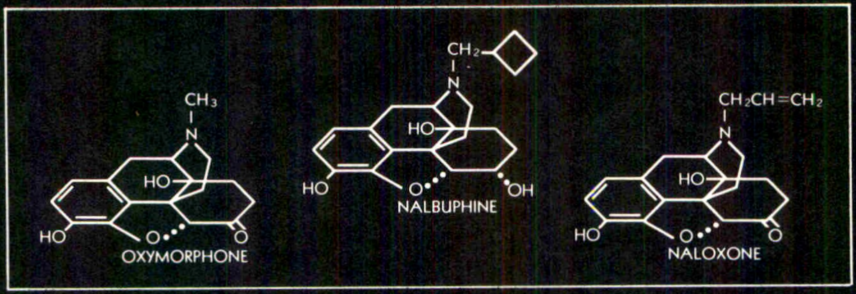
new

NUBAIN®

nalbuphine HCl

OFFERS LOW POTENTIAL FOR ABUSE

- NUBAIN requires no special storage or additional paperwork beyond your normal order or prescription.
- The unique properties of NUBAIN may be found in its molecular structure.



- Certain substances, such as NARCAN® (naloxone HCl), counteract or antagonize the effects and side effects of potent narcotics, such as morphine or NUMORPHAN® (oxymorphone HCl). NUBAIN was designed to incorporate important molecular features of the antagonist NARCAN and the potent analgesic NUMORPHAN, resulting in a drug with strong analgesia but limited abuse potential.

And a lower respiratory effect

- At dosages of 10 mg/70 kg, NUBAIN causes respiratory depression comparable to that of morphine. In contrast to morphine, higher doses of NUBAIN do not increase respiratory depression appreciably (see Precautions).

NARCAN is an Endo registered U.S. trademark.

NUMORPHAN is an Endo registered U.S. trademark.

Please see complete prescribing info[illegible]ation on last page of this adve[illegible]sement.

A clinical summary:

27 investigations evaluated more than 1,000 medical and surgical patients in regard to the effect of NUBAIN upon acute or chronic pain. Among these studies are the following, which highlight important areas of analgesic use:

- ORTHOPEDICS—this study encompassed 52 patients and compared NUBAIN to meperidine. Treatment varied from 1 to 40 days. NUBAIN was found to deliver satisfactory analgesia with no overt evidence of physical tolerance.
- CANCER—this study encompassed 37 patients treated for 1 to 186 days. Many of the patients stabilized on I.M. NUBAIN received dosages every 6-8 hours.
- OBSTETRICS—four double-blind studies were conducted encompassing 159 patients in labor. I.M. NUBAIN was compared to I.M. meperidine. Analgesically, both drugs were deemed similar (10-15 mg NUBAIN equal to 75-113 mg meperidine). Neonates did equally well on both drugs, but there is a possibility that either drug can produce depressive effects in the fetus or neonate. Mothers treated with NUBAIN had fewer side effects, and hospital personnel liked NUBAIN.
- Please see full prescribing information, including a complete discussion of adverse reactions, on following page.

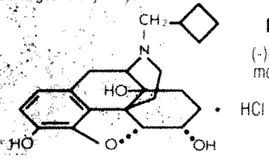
NUBAIN® (nalbuphine HCl)

Analgesia comparable to morphine, with important differences.

new NUBAIN® nalbuphine HCl

DESCRIPTION

NUBAIN (nalbuphine hydrochloride) is a synthetic narcotic agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used narcotic antagonist, naloxone, and the potent narcotic analgesic, oxymorphone.



NALBUPHINE HYDROCHLORIDE

(-)-17-(cyclobutylmethyl)-4, 5α-epoxy ⊂ morphinan-3, 6α, 14-triol,hydrochloride

Each ml of the injectable aqueous solution of NUBAIN contains 10 mg of nalbuphine hydrochloride.

ACTIONS

NUBAIN is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis.

Its onset of action occurs within 2 to 3 minutes after intravenous administration, and in less than 15 minutes following subcutaneous or intramuscular injection. The plasma half-life of nalbuphine is 5 hours and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours.

The narcotic antagonist activity of NUBAIN is one-fourth as potent as nalorphine and 10 times that of pentazocine.

INDICATIONS

For the relief of moderate to severe pain. NUBAIN can also be used for preoperative analgesia, as a supplement to surgical anesthesia, and for obstetrical analgesia during labor.

CONTRAINDICATIONS

NUBAIN should not be administered to patients who are hypersensitive to it.

WARNINGS

Drug Dependence NUBAIN has been shown to have a low abuse potential which is approximate to that of pentazocine. When compared with drugs which are not mixed agonist-antagonists, it has been reported that nalbuphine's potential for abuse would be less than that of codeine and propoxyphene. Psychological and physical dependence and tolerance may follow the abuse or misuse of nalbuphine. Therefore, caution should be observed in prescribing it for emotionally unstable patients, or for individuals with a history of narcotic abuse. Such patients should be closely supervised when long-term therapy is contemplated.

Care should be taken to avoid increases in dosage or frequency of administration which in susceptible individuals might result in physical dependence.

Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection.

Use in Ambulatory Patients NUBAIN may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, NUBAIN should be administered with caution to ambulatory patients who should be warned to avoid such hazards.

Use in Emergency Procedures Maintain patient under observation until recovered from NUBAIN effects that would affect driving or other potentially dangerous tasks.

Use in Children Clinical experience to support administration to patients under 18 years is not available at present.

Use in Pregnancy (other than labor) Safe use of NUBAIN in pregnancy has not been established. Although animal reproductive studies have not revealed teratogenic or embryotoxic effects, nalbuphine should only be administered to pregnant women when, in the judgement of the physician, the potential benefits outweigh the possible hazards.

Use During Labor and Delivery NUBAIN can produce respiratory depression in the neonate. It should be used with caution in women delivering premature infants.

Head Injury and Increased Intracranial Pressure The possible respiratory depressant effects and the potential of potent analgesics to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, NUBAIN should be used in these circumstances only when essential, and then should be administered with extreme caution.

Interaction With Other Central Nervous System Depressants Although NUBAIN possesses narcotic antagonist activity, there is evidence that in nondependent patients it will not antagonize a narcotic analgesic administered just before, concurrently, or just after an injection of NUBAIN. Therefore, patients receiving a narcotic analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUBAIN may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced

PRECAUTIONS

Impaired Respiration At the usual adult dose of 10 mg/70 kg, NUBAIN causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of NUBAIN. Respiratory depression induced by NUBAIN can be reversed by NARCAN® (naloxone hydrochloride) when indicated. NUBAIN should be administered with caution at low doses to patients with impaired respiration (e.g., from other medication, uremia, bronchial asthma, severe infection, cyanosis or respiratory obstructions).

Impaired Renal or Hepatic Function Because NUBAIN is metabolized in the liver and excreted by the kidneys, patients with renal or liver dysfunction may overreact to customary doses. Therefore, in these individuals, NUBAIN should be used with caution and administered in reduced amounts.

Myocardial Infarction As with all potent analgesics, NUBAIN should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Tract Surgery As with all narcotic analgesics, NUBAIN should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

ADVERSE REACTIONS

The most frequent adverse reaction in 1066 patients treated with NUBAIN is sedation (381, 36%).

Less frequent reactions are: sweaty/clammy (99, 9%), nausea/vomiting (68, 6%), dizziness/vertigo (58, 5%), dry mouth (44, 4%), and headache (27, 3%).

Other adverse reactions which may occur (reported incidence of 1% or less) are:

CNS Effects nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine.

Cardiovascular Hypertension, hypotension, bradycardia, tachycardia.

Gastrointestinal Cramps, dyspepsia, bitter taste.

Respiration Depression, dyspnea, asthma.

Dermatological Itching, burning, urticaria.

Miscellaneous Speech difficulty, urinary urgency, blurred vision, flushing and warmth.

DOSAGE AND ADMINISTRATION

The usual recommended adult dose is 10 mg for a 70 kg individual, administered subcutaneously, intramuscularly or intravenously; this dose may be repeated every 3 to 6 hours as necessary. Dosage should be adjusted according to the severity of the pain, physical status of the patient, and other medications which the patient may be receiving. (See Interaction with Other Central Nervous System Depressants under WARNINGS.) In non-tolerant individuals, the recommended single maximum dose is 20 mg, with a maximum total daily dose of 160 mg.

Patients Dependent on Narcotics Patients who have been taking narcotics chronically may experience withdrawal symptoms upon the administration of NUBAIN. If unduly troublesome, narcotic withdrawal symptoms can be controlled by the slow intravenous administration of small increments of morphine, until relief occurs. If the previous analgesic was morphine, meperidine, codeine, or other narcotic with similar duration of activity, one-fourth of the anticipated dose of NUBAIN can be administered initially and the patient observed for signs of withdrawal, i.e., abdominal cramps, nausea and vomiting, lacrimation, rhinorrhea, anxiety, restlessness, elevation of temperature or piloerection. If untoward symptoms do not occur, progressively larger doses may be tried at appropriate intervals until the desired level of analgesia is obtained with NUBAIN.

Management of Overdosage The immediate intravenous administration of NARCAN® (naloxone hydrochloride) is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

The administration of single doses of 72 mg of NUBAIN intramuscularly to eight normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria.

HOW SUPPLIED

NUBAIN® (nalbuphine hydrochloride) injection for intramuscular, subcutaneous, or intravenous use (10 mg/ml) is available in:

NDC #0056-0385 10 mg/ml, 1 ml ampuls (box of 10)
NDC #0056-0384 10 mg/ml, 2 ml ampuls (box of 10)
NDC #0056-0386 10 mg/ml, 10 ml vials

Each ml contains 10 mg nalbuphine hydrochloride, 0.1% sodium chloride, 0.94% sodium citrate, 1.26% citric acid anhydrous, 0.1% sodium metabisulfite, and 0.2% of a 9:1 mixture of methylparaben and propylparaben as preservative; pH is adjusted with hydrochloric acid.

6094-1 Rev. March 1979

Endo Laboratories, Inc.
Subsidiary of the DuPont Company
Garden City, New York 11530

DU PONT
REG. U.S. PAT. & TM. OFF.

NUBAIN is an Endo Registered U.S. Trademark
NARCAN is an Endo Registered U.S. Trademark

EDO-403B579

The AO® Short Colonoscope offers you increased diagnostic capability with greater patient comfort.

See demonstration at Booth 954
American College of Surgeons
Chicago, October 22 to 25.

Conventional proctoscopes frequently can't reach beyond the recto-sigmoid flexure of the colon, where disease often occurs. With the flexible, 65cm AO Short Colonoscope, you can negotiate that flexure and obtain a clear view of the sigmoid colon area.

And you can do this with greater patient comfort, thanks to the small diameter and flexibility of the fiber optic length. The SC-4 is easy to insert and easy to maneuver. There's no need for a special examining table or awkward knee-chest position. Your patient relaxes in the left lateral position for quick, thorough examination with minimal discomfort.

The AO Short Colonoscope features four-way control and excellent viewing optics. It also includes capabilities for biopsy, suction, cytology, and insufflation.

And it costs much less than other colonoscopes.

AO®
American Optical

Scientific Instrument Division
Southbridge, MA 01550
(617) 765-9711, ext. 2445

American Optical—Fiber Optics, Southbridge, MA 01550.
NAME ____________________
ADDRESS ____________________
CITY ____________ STATE ____________ ZIP ____________
PHONE ____________________ EXT. ____________

☐ Arrange a demonstration.

☐ Send more information.

For ulcerative proctitis patients wh

CORTIFOAM®
(hydrocortisone acetate 10% rectal foam)

Contains hydrocortisone acetate 10% as the sole active ingredient in 20 GMs of a foam containing propylene glycol, ethoxylated stearyl alcohol, polyoxyethylene-10-stearyl ether, cetyl alcohol, methyl and propyl parabens, triethanolamine, water and inert propellants.

Each application delivers approximately 900 mg. of foam containing 80 mg. of hydrocortisone (90 mg. of hydrocortisone acetate)

Clinical pharmacology: CORTIFOAM provides topical administration of an anti-inflammatory corticosteroid as adjunctive therapy of ulcerative proctitis

Indications: CORTIFOAM is indicated as adjunctive therapy in the topical treatment of ulcerative proctitis of the distal portion of the rectum in patients who cannot retain hydrocortisone or other corticosteroid enemas.

Direct observations of methylene blue-containing foam have shown staining no higher than 10 centimeters into the rectum

Contraindications: Local contraindications to the use of intrarectal steroids include obstruction, abscess, perforation, peritonitis, fresh intestinal anastomoses, extensive fistulas and sinus tracts.

Tuberculosis (active, latent or questionably healed), ocular herpes simplex and acute psychosis are usually considered absolute contraindications to the use of corticosteroids

Relative contraindications include active peptic ulcer, acute glomerulonephritis, myasthenia gravis, osteoporosis, diverticulitis, thrombophlebitis, psychic disturbances, pregnancy, diabetes, hyperthyroidism, acute coronary disease, hypertension, limited cardiac reserve, and local or systemic infections, including fungal or exanthematous diseases. Where these conditions exist, the expected benefits from steroid therapy must be weighed against the risks involved in its use.

Pregnancy is a relative contraindication to corticosteroids, particularly during third trimester. If corticosteroids must be administered in pregnancy, watch newborn infant closely for signs of hypoadrenalism, and administer appropriate therapy if needed

Warning: Do not insert any part of the aerosol container into the anus. Contents of the container are under pressure, but not flammable. Do not burn or puncture the aerosol container. Store at room temperature—not over 120°F

Because CORTIFOAM is not expelled, systemic hydrocortisone absorption may be greater from CORTIFOAM than from corticosteroid enema formulations. If there is no evidence of clinical or proctologic improvement within two or three weeks after starting CORTIFOAM therapy, or if the patient's condition worsens, discontinue the drug.

Precautions: Steroid therapy should be administered with caution in patients with severe ulcerative disease because these patients are predisposed to perforation of the bowel wall. Where surgery is imminent, it is hazardous to wait more than a few days for a satisfactory response to medical treatment. General precautions common to all corticosteroid therapy should be observed during treatment with CORTIFOAM. These include gradual withdrawal of therapy to allow for possible adrenal insufficiency and awareness to possible growth suppression in children. Patients should be kept under close observation, for, as with all drugs, rare individuals may react unfavorably under certain conditions. If severe reactions or idiosyncrasies occur, steroids should be discontinued immediately and appropriate measures instituted. Do not employ in immediate or early postoperative period following ileorectostomy

Adverse reactions: Corticosteroid therapy may produce side effects which include moon face, fluid retention, excessive appetite and weight gain, abnormal fat deposits, mental symptoms, hypertrichosis, acne, ecchymosis, increased sweating, pigmentation, dry scaly skin, thinning scalp hair, thrombophlebitis, decreased resistance to infection, negative nitrogen balance with delayed bone and wound healing, menstrual disorders, neuropathy, peptic ulcer, decreased glucose tolerance, hypopotassemia, adrenal insufficiency, necrotizing angiitis, hypertension, pancreatitis and increased intraocular pressure. In children, suppression of growth may occur. Increased intracranial pressure may occur and

an't retain the steroid enema...

Frequently your ulcerative proctitis patient can't retain the steroid enema: when the patient needs to be ambulatory; when the patient is in the early stages of therapy; when a steroid enema triggers the onset of tenesmus, or when sphincter control is weak.

Now there's an alternative to the retention enema—Cortifoam® (hydrocortisone acetate 10%) rectal foam. With Cortifoam, the steroid is kept in contact with the inflamed mucosa by a muco-adhesive foam base. Unlike retention enemas, Cortifoam can be administered at any time convenient to the patient in just 30 seconds—even while standing. Following administration, Cortifoam requires no lengthy period of reclining, no struggle to retain medication. And it usually won't leak or stain even in active patients. "This form of treatment is better tolerated since it does not provoke the tenesmus or urgency that often accompany a fluid enema."*

Finally, Cortifoam is more economical per application than commercially-available steroid enemas.

So when you need an alternative for ulcerative proctitis patients who can't retain steroid enemas, now you can prescribe one—Cortifoam.

*Korelitz, B.I.: *Hospital Medicine* 14:8-34, March, 1978

Reed & Carnrick/Kenilworth, New Jersey 07033

The easy-to-retain alternative.

Cortifoam®

(hydrocortisone acetate 10%) rectal foam

possibly account for headache, insomnia and fatigue. Subcapsular cataracts may result from prolonged usage. Long-term use of all corticosteroids results in catabolic effects characterized by negative protein and calcium balance. Osteoporosis, spontaneous fractures and aseptic necrosis of the hip and humerus may occur as part of this catabolic phenomenon. Where hypopotassemia and the other symptoms associated with fluid and electrolyte imbalance call for potassium supplementation and salt-poor or salt-free diets, these may be instituted and are compatible with diet requirements for ulcerative proctitis.

Administration and dosage: Usual dose is one applicatorful once or twice daily for two or three weeks, and every second day thereafter, administered rectally. The patient direction package with the applicator describes how to use the aerosol container and applicator. Satisfactory response usually occurs within five to seven days marked by a decrease in symptoms. Symptomatic improvement in ulcerative proctitis should not be used as the sole criterion for evaluating efficacy. Sigmoidoscopy is also recommended to judge dosage adjustment, duration of therapy and rate of improvement.

How supplied: CORTIFOAM is supplied in an aerosol container with a special rectal applicator. Each applicator delivers approximately 900 mg. of foam containing approximately 80 mg. of hydrocortisone as 90 mg. of hydrocortisone acetate. The aerosol container will deliver a minimum of 14 applications.

Get the inside story on the latest techniques.

Naumann

Head & Neck Surgery

Vol. I: Face and Facial Skull

2nd Edition

If you're familiar with the general surgical and clinical aspects of disorders of the head and neck, but require more detailed information on special surgical techniques, **Naumann** is the book for you. Organized practically for the operating table, it provides you with detailed illustrations of operative methods backed by supportive textual information. The authors, along with contributors from a variety of specialties, present explicit descriptions of established procedures and in some cases, alternative successful methods are mentioned. Complete bibliographic references are furnished for your convenience. It's a book you'll want to refer to often. Order today.

Edited by **H.H. Naumann**, MD, Prof., Director, Universitats-Hals-Nasen-Ohren-Klinik, Munchen; and co-edited by **R.A. Buckingham**, Prof. of Otolaryngology, Abraham Lincoln School of Medicine, Univ. of Illinois, Chicago. About 2400 pp. (Vol. 1 of a 4 vol. set). Ready soon. **Order #6663.**

Hendrickson & Kempson

Surgical Pathology of the Uterine Corpus

Major Problems in Pathology, 12

This useful monograph on uterine tumors is profusely illustrated with photomicrographs of most examples of uterine pathology. It will also serve as a much needed atlas of endometrial and myometrial pathology. Included in this comprehensive volume is information on: congenital uterine abnormalities, uterine bleeding and infertility, endometritis, and much more!

By **Michael R. Hendrickson**, MD, Asst. Prof. of Pathology, Surgical Pathology Laborabory, Stanford Univ. Medical Center; and **Richard L. Kempson**, MD, Prof. of Pathology, Co-Director of Surgical Pathology, Stanford Univ. Medical Center. About 520 pp. 270 ill. About $36.00. Ready soon. **Order #4644-1.**

Hill

Outpatient Surgery

2nd Edition

A guide to the management of surgical problems in the outpatient, this book covers the entire field of surgery and its related specialties. Diagnostic and therapeutic considerations outlined for conditions requiring longer periods of hospitalization and major surgery provide helpful background information. Techniques for scores of minor surgical procedures are described and illustrated in detail. And, alternate approaches are sometimes indicated when the same condition is treated by two physicians in separate specialties.

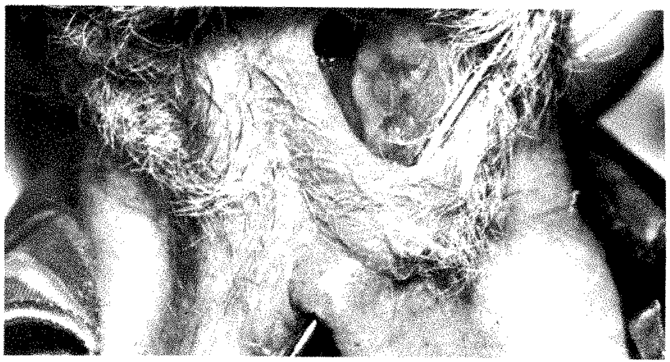
By **George J. Hill, II**, MD, Prof. and Chairman, Dept. of Surgery, Associate Dean for Clinical Affairs, Marshall Univ. School of Medicine, Huntington, West Virginia. About 1200 pp. About $50.00. Ready soon. **Order #4676-X.**

Lick

Color Atlas of Surgery

This illustrated documentation of surgical, diagnostic-clinical and intraoperative findings fills a long-existing gap in the medical literature. Focusing on information concerning surgical findings, it includes numerous excellent illustrations of gross pathology which help to identify the diagnostic warning signals of various diseases. Every illustrated page has been conceived as a complete unit—and the corresponding text page provides a concise, general surgical-clinical introduction to the respective subject.

By Prof. **Dr. Rainer F. Lick**, Chief, Director of Medicine, Univ. of Wurzberg, Coburg, Germany. About 530 pp. 1000 process color ill. About $75.00. Ready soon. **Order #5767-2.**



Conley

Complications of Head and Neck Surgery

Dr. John Conley of Columbia University and 12 other prominent surgeons have merged their expertise to produce this comprehensive otolaryngologic study. Topics covered include such prevalent problems as hemorrhage, infection, thromboembolism, and complications of specific head and neck operative procedures. Otolaryngologists, maxillofacial, plastic, head and neck, and general surgeons will find this new book especially helpful.

Edited by **John Conley**, MD. About 525 pp., 215 ill. About $32.00. Ready soon. **Order #2649-1.**

Cooley & Wukasch

Techniques in Vascular Surgery

This current summary provides a ready source of information on today's vascular surgical techniques. New concepts in the use of grafts and graft materials, techniques of anastomosis and the treatment of all types of vascular diseases are a few of the topics discussed. Concise text accompanied by clear, to-the-point illustrations and pertinent references add to a long list of valuable features.

By **Denton A. Cooley**, MD, Surgeon-in-Chief Clinical Prof. of Surgery, The Texas Heart Institute of St. Luke's Episcopal, Houston, Texas; and **Don C. Wukasch**, MD, Attending Surgeon, Clinical Associate Prof., Texas Heart Institute. 282 pp. 102 ill. About $30.00. Ready soon. **Order #2700-5.**

Surgical Clinics

First hand reports on new developments in surgery...strictly practice-applicable information...in-depth, up-to-the minute coverage...fresh perspectives...references to recent literature...and better yet, a year's subscription to the **Surgical Clinics of North America** costs less than a year's subscription to your daily newspaper! 1979 symposia include:

Feb. **Endocrine Surgery**
April **Surgical Aspects of Immunology**
June **Advances in Small Hospital Care**
Aug. **Peripheral Vascular Surgery**
Oct. **Morbid Obesity**
Dec. **New Methods of Treatment of Gastrointestinal Diseases**

Published bi-monthly. Hardbound. Illustd. Each issue average 275 pages. Yearly subscription $30.00 (Single copies $10.50).

To order titles on 30-day approval, enter order number & author:

ANS 9/79

☐ Start my subscription to the Surgical Clinics with the ____________ issue.

☐ Only send the ____________ issue(s) of the Surgical Clinics.

AU:

AU:

AU:

FULL NAME ____________

POSITION & AFFILIATION (IF APPLICABLE) ____________

ADDRESS ____________

CITY STATE ZIP ____________

☐ check enclosed (send postpaid) ☐ bill me (plus postage and handling) Prices differ outside US and are subject to change

W.B. Saunders Co.

P.O. Box 207, Philadelphia, PA 19105
1 Goldthorne Avenue, Toronto, Ontario M8Z 5T9, Canada
1 St. Anne's Road, Eastbourne, East Sussex BN21 3UN, England
9 Waltham Street, Artarmon NSW 2064, Australia

Chinese Experience in the Surgical Treatment of Carcinoma of the Esophagus

WU YING-K'AI, M.B., Ch.B., HUANG KUO-CHUN, M.D.

From the Fu Wai Hospital and the Cancer Institute,
Chinese Academy of Medical Sciences,
Peking, People's Republic of China

CARCINOMA OF THE ESOPHAGUS is one of the common cancers among the Chinese, especially in North China. Chinese thoracic surgeons have taken surgical treatment of esophageal cancer as one of their main tasks for the past 40 years. The first successful esophageal resection for carcinoma with intrathoracic esophagogastrostomy in China was performed in 1940.[1] Since then, this operation has been done in large numbers of hospitals as years go by. Now, it has become a common practice by thoracic surgeons as well as general surgeons in many clinics, including medical centers and provincial and county hospitals. The clinical experience so accumulated is extensive and divergent. In this report, we shall merely present a brief summary of some of the main points.

Resectability Rate

During the two decades between 1940 and 1960, resectability rate for esophageal carcinoma had been relatively low. We compiled data from 13 Chinese clinics in 1961 (Table 1). In a collective series of 5412 cases of carcinoma of the esophagus and gastric cardia, the resectability rate was 39.1% by number of admissions and 59.5% by number of explorations.[2] At the Fu Wai Hospital during the period 1962–1968, in a series of 778 cases the resectability rate had increased to 58.5% by number of admissions and 69.2% by number of explorations.[3] Resectability rate in more recently reported series has further increased to over 80%.[4–8] In one series from the county hospital of Linhsien of Honan province, where a number of very early esophageal cancers had been operated upon on the basis of frequent population surveys, the resectability rate in a series of 1228 cases was as high as 94.1%.[9]

Operative Mortality Rate

The operative risk for esophageal cancer had been quite high for many years in the past. In China, the operative mortality rate for resection of carcinoma of the esophagus was over 25% in the early years. By 1960, it had come down to around 10%.[2] It has further decreased to about 3–5% in recent years.[4,5,7,8] Our own statistics have shown a steady decline during the past 30 years (Table 2).

Remote Results

For a long time in the past, there had been a prevailing pessimism in the medical profession about the value of surgical treatment of esophageal cancer. Our experience in China does not support such an opinion. Follow-up statistics from a number of Chinese clinics have shown an average five-year survival rate of around 25%. Those of the recent series are in the neighborhood of 30–40% (Table 3). Special comment is to be made here about the Linhsien experience.[9] In a series of 250 resections of carcinoma of the esophagus, the five-year survival rate was 44%, and in 163 cases of very early esophageal cancers discovered during population survey, there was only one postoperative recurrence 9 years after the resection. Of the 31 patients operated upon five years previously, 28 survived over the five-year period, with a five-year survival rate of 90.3%. These facts point to the conclusion that surgical treatment for esophageal carcinoma is as effective as surgery for cancers of any other sites.

Of the factors affecting the remote results of surgical treatment of carcinoma of the esophagus, the site and extent of the cancer have important bearings. In our series of 428 resections of carcinoma of the esophagus and 157 resections of cancer of the gastric cardia operated on between 1940 and 1961, the five-year survival rate for cancers of the lower third of the esophagus was 31.3%, that for the gastric cardia was 22.6% and that for the upper and middle thirds of the esophagus was only 14.3% (Fig. 1).[2] Another series

---

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

0003-4932/79/0900/0361 $00.75 © J. B. Lippincott Company

TABLE 1. *Resectability Rate of Carcinoma of the Esophagus**

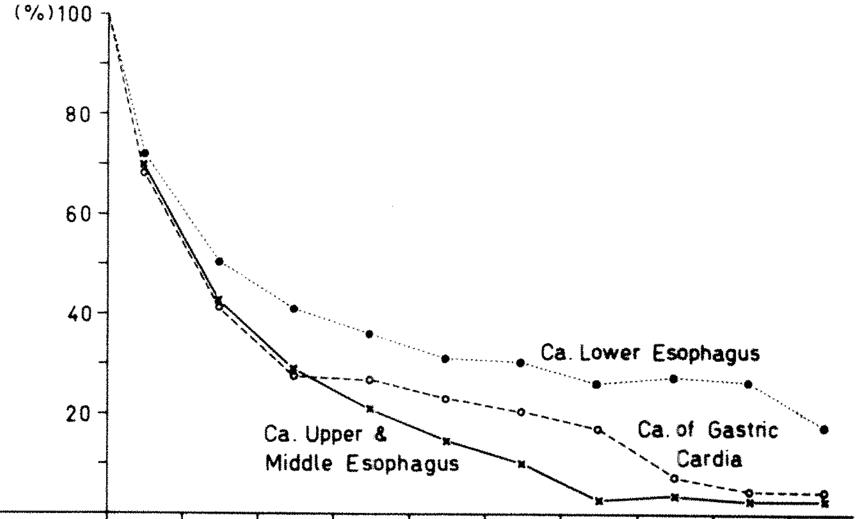
Source of Data	Year of Operation	No. of Explorations	No. of Resections	Per Cent Resectability Rate
Compiled data from 13 Chinese clinics[2]	1940–1961	3553	2114	59.5
Fu Wai Hospital[3]	1962–1968	669	463	69.2
4th Affiliated Hospital, Ho Pei Medical College[4]	1952–1976	2226	1754	78.8
Peking Medical College Hospitals[5]	1953–1973	818	664	81.2
Cancer Institute, Chinese Academy of Medical Sciences[7]	1958–1976	1331	1119	84.1
Shanghai Chest Hospital[8]	1957–1978	3309	2706	81.7
Linhsien County Hospital, Honan[9]	1964–1974	1228	1156	94.1

* In some series, carcinoma of gastric cardia were also included.

TABLE 2. *Operative Mortality Rate of Resection of Carcinoma of the Esophagus*

Source of Data	Year of Operation	No. of Resections	No. of Postop. Deaths	Per Cent Operative Mortality Rate
Fu Wai Hospital and Related Hospitals*	1940–1949	56	14	25.0
	1950–1965	603	38	6.3
	1966–1968	92	2	2.2
4th Affiliated Hospital, Ho-pei Medical College†	1952–1958	41	9	22.0
	1959–1965	494	72	14.6
	1966–1976	2242	66	2.9
Cancer Institute, Chinese Academy of Medical Sciences†	1958–1976	1119	40	3.6
Peking Medical College Hospitals*	1953–1973	664	37	5.6
Shanghai Chest Hospital*	1957–1978	2706	171	6.4

* Including all hospital deaths following resection.
† Including all deaths within 30 days after resection.



Year after Operation	1	2	3	4	5	6	7	8	9	10
Upper & Mid. Esophagus	69.4	41.7	28.2	21.1	14.3	10.5	2.8	3.1	3.6	3.7
Lower Esophagus	71.7	50.0	41.0	36.5	31.3	30.8	26.3	27.8	27.3	17.9
Gastric Cardia	68.6	41.4	27.6	27.0	22.6	20.7	17.2	7.7	4.2	4.2

FIG. 1. Survival rate following resection of carcinoma of esophagus and gastric cardia.

TABLE 3. *Five-year Survival Rate Following Resection of Carcinoma of the Esophagus*

Source of Data	Year of Operation	No. of Resections Performed 5 Years Previously	No. of Cases Surviving 5 Years	Per Cent 5-Year Survival Rate
Wu and associates	1940–1961	97	22	22.7
Fourth Affiliated Hospital, Hopei Medical College[4]	1966–1971	625	106	25.5
Cancer Institute, Chinese Academy of Medical Sciences[7]	1958–1972	485	142	29.3
Shanghai Chest Hospital[8]	1957–1973	1040	276	26.6
Peking Medical College Hospitals[5]	1957–1973	664	164	24.7
Linhsien County Hospital, Honan[9]	1964–1974	250	110	44.0

TABLE 4. *Five-year Survival Rate Following Resection of Carcinoma of the Esophagus (Peking Medical College Hospitals, 1953–1973)*

	Site of Cancer			Extent of Cancer		Lymphnode Metastasis	
	Upper Esophagus	Middle Esophagus	Lower Esophagus	Limited to Esophageal Wall	Infiltrated Beyond Esophageal Wall	Negative	Positive
No. cases	28	327	220	451	55	305	208
No. 5-year survivals	3	87	72	147	4	146	13
5-year survival rate	10.7%	26.6%	32.7%	32.6%	7.3%	47.9%	6.3%

from the Peking Medical College hospitals[5] showed that those cancers limited within the boundaries of the esophagus had a five-year survival rate of 32.6%, as against a 7.3% five-year survival rate when the cancer had infiltrated beyond the boundary of the esophageal wall. When there was no lymph node metastasis, the five-year survival rate was 47.9%, while in those with positive lymph node metastasis, the five-year survival rate was only 6.3% (Table 4). In 95 cases of carcinoma of lower third of the esophagus without lymph node

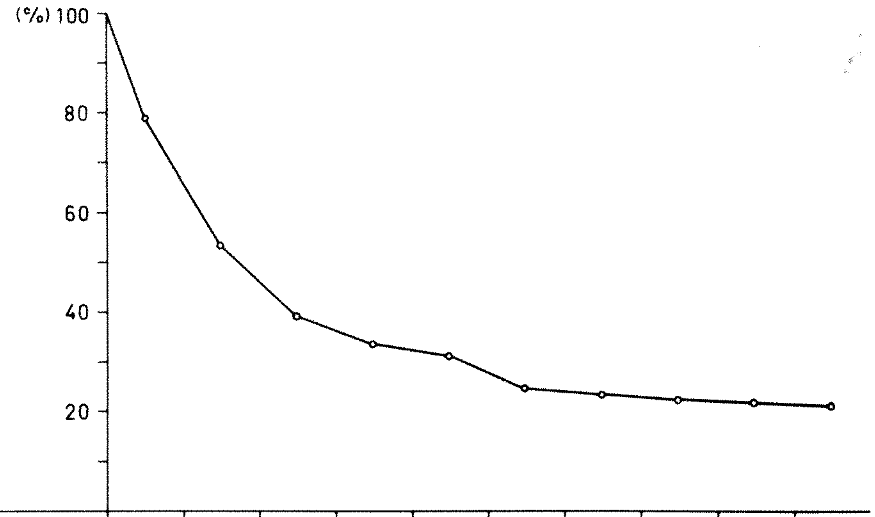


FIG. 2. Survival rates following preoperative radiation therapy and resection for carcinoma of the esophagus.

Year after Operation	1	2	3	4	5	6	7	8	9	10
No. of Resections	334	321	291	248	212	195	192	186	179	178
No. of Survivals	260	170	114	83	67	48	44	42	39	39
Survival Rate(%)	77.8	53.0	39.2	33.5	31.6	24.6	22.9	22.6	21.8	21.9

metastasis, the five-year survival rate was as high as 64.2%.

Technical Considerations

Of the various surgical approaches and methods of reconstruction of the alimentary passage following resection of carcinoma of the esophagus, most Chinese thoracic surgeons employ the left posterolateral thoracotomy and a one-stage extensive esophagectomy followed by esophagogastrostomy. Efforts are made to remove all the accessible lymph nodes in the mediastinum and in the epigastric region together with the esophagus and the gastric cardia. For some years in the past, we made a general requirement to include in the resection a normal segment of the esophagus of about 5–6 cm proximal to the palpable upper limit of the esophageal cancer. Subsequent study showed such a conservative resection was often inadequate, as pathologic examination of the surgical specimens revealed cancer cells in the upper edge of the resected esophagus in over 10% of cases. During recent years, we have advocated more extensive esophagectomy. For cancers of the lower esophagus, the esophagogastrostomy after resection is often performed at the supraaortic level. In cancers of the middle segment of the esophagus, the esophagogastrostomy following resection is often done at the level of the dome of the pleural cavity; when the cancer has extended to above the level of the aortic arch, the esophagogastrostomy is to be performed in the neck.

The esophagogastrostomy following esophageal resection is usually performed by open anastomosis with direct sutures in two layers. The incidence of postoperative leakage of the anastomosis has been in the range of 3–5%. During recent years, a stapler-type suturing apparatus for esophagogastrostomy has been used in several clinics in China. Thoracic surgeons of the Kiangsu Hospital[10] and Cancer Hospital of Honan Province[11] each reported series of 100 and 275 cases, respectively, of esophageal resections and esophagogastrostomy using the suture apparatus with no anastomosis leakage, but there were a few cases of mild stenosis of the anastomosis stoma in the early postoperative period. Further improvement of the instrument and in the technique of its use are under way.

Preoperative Radiation Therapy

At the Cancer Institute of the Chinese Academy of Medical Sciences, the use of preoperative radiation therapy combined with surgical resection had been practiced in 408 cases of carcinoma of the esophagus. Most of the cancers were clinically estimated to be of borderline resectability. The lesion was in the upper and middle esophagus in 80% and longer than 5 cm in 81.5%, and the growth had already extended beyond the boundary of the esophagus in 70.2%. Following an average preoperative radiation of 2000–4000 rads, resection was accomplished in 334 cases, with a resectability rate of 81.9%. In 212 patients operated upon five years previously, the five year survival rate was 31.6%. In 178 cases, a ten year survival rate of 21.9% was noted (Fig. 2). No unusual technical difficulty was encountered during the operation. The operative mortality rate for the 334 resections was 3.9%, as against an operative mortality rate of 3% in 736 resections of esophageal cancer without preoperative radiation during the same period at the same institute. These figures speak rather favorably for the value of the preoperative radiation therapy. We are of the opinion that this type of combined therapy is to be recommended for carcinoma of the esophagus of questionable resectability.

Concluding Remarks

Much progress has been made in the surgical treatment of carcinoma of the esophagus in China as well as in many other countries in the past 20 years. With reasonably early diagnosis, it is within the ability of the thoracic surgeons today to achieve a resectability rate of 75–85% and to keep the operative mortality rate below 5% and a five-year survival rate of 30–40%. With careful selection of patients for operation and proper use of radiation and other adjunct therapy, even more encouraging results are possible. Efforts for further improvement may be directed toward early diagnosis and refinement in operative techniques, such as the use of microsurgery in reconstruction of the esophagus and further development of instrumentation for the esophagogastric anastomosis.

References

1. Wu, Y. K. and Loucks, H. H.: Surgical Treatment of Carcinoma of the Esophagus. Chin. Med. J., 60:1–33, 1941.
2. Wu Ying-Kái, Huang Kuo-Chun and Chang Wei: Carcinoma of Esophagus and Gastric Cardia, Chapter 10, Shanghai Scientific and Technologic Press, 1965 (in Chinese).
3. Wu Ying-Kái and Huang Kuo-Chun: Chest Surgery, Chapter 23, People's Health Publisher, Peking, 1974 (in Chinese).
4. The Fourth Affiliated Hospital, Hopei Medical College: Remote Result of Surgical Treatment of Carcinoma of the Esophagus, Cancer Research, Vol. 1, 1978 (in Chinese).
5. Li Yeh-min et al.: Long Term Results of Surgical Treatment of Carcinoma of the Esophagus and Gastric Cardia. (Unpublished data from Peking Medical College Hospitals) 1979.
6. Cancer Institute, Chinese Academy of Medical Sciences: Surgical Treatment of Carcinoma of Esophagus and Gastric Cardia, Chin. Med. J., 1:60–63, 1975.
7. Huang Kuo-chun et al.: Surgical Treatment of Carcinoma of the Esophagus and Gastric Cardia: Analysis of 2004 Cases, to be published.
8. Huang Ao-lin et al.: Surgical Treatment of Carcinoma of the Esophagus and Gastric Cardia, Statistics from the Shanghai Chest Hospital, 1957 to 1978. (Unpublished data).

9. Collaborating Group for Research on Esophageal Cancer, Linhsien Country, Honan: Early Diagnosis and Surgical Treatment of Esophageal Cancer Under Rural Conditions. Chin. Med. J., 2:113–116, 1976.
10. Wu, Wei-chi et al.: Esophagogastrostomic Anastomosis Instrument. Chin. Med. J., 4:204–211, 1978.
11. Shao Ling-fang: Apparatus for Esophago-Gastric anastomosis, unpublished data.

DISCUSSION

DR. CARL E. LISCHER (St. Louis, Missouri): When Dr. Wu came to St. Louis just before World War II, carcinoma of the esophagus was a medical curiosity at Barnes Hospital. I think Dr. Phemister did the first resection of a carcinoma of the esophagus in this country, and shortly thereafter Dr. Evarts Graham did two. About two weeks after Dr. Wu's arrival in St. Louis, Dr. Womack, at his weekly surgical pathology conference presented the two patients with carcinoma of the esophagus. Towards the end of the conference, in a very modest and quiet manner, Dr. Wu said, "I just happen to have a couple of slides." So, he got up and discussed his own personal experience with some ten patients. From then on Dr. Graham had the highest admiration for Dr. Wu, who always went about his work in a quiet, modest way.

After 18 months, I was still calling Dr. Wu "Y. K." and then I found out that his name is Ying Kai. Only now have I learned, 37 years later, that the surname always comes first, so it's Wu Ying Kai prefixed by Doctor or Professor. I still call him "Y. K.," but I'm told that's quite impolite. He has told me that in China, close friends of his age group would address him properly as "old Wu."

In the audience, there are two other people who were house officers at Barnes along with Dr. Wu: Drs. Eckert and Bruneau.

I hope that in the future you come to many meetings. This would be a great pleasure for me and I'm sure that I am expressing the wishes of the entire association.

Specific Active Immunotherapy for Melanoma

H. F. SEIGLER, M.D., E. COX, F. MUTZNER, L. SHEPHERD, E. NICHOLSON, W. W. SHINGLETON

The most effective immunization historically has been active immunization against a specific disease process. We report here the results of specific active immunization of 719 patients with invasive melanoma. The patients were sequentially immunized with approximately 2.5 × 10^7 x-irradiated, neuraminidase treated melanoma cells and BCG was used for its adjuvant effect. The sites of primary tumor location included trunk (42%), extremity (35%), head and neck (15%), unknown (3%), eye (2%) and mucocutaneous (1%). Two hundred thirty-six Clark's Level III patients with Stage I disease experienced an 88% survival ar four years while 47 Stage II patients had an observed survival of 82% during this same time period. Very similar statistics were observed for 124 State I Clark's Level IV patients and 70 Stage II patients. Nineteen and 26 Clark's Level V patients with Stage I and Stage II disease realized a 100% and 55% observed survival at four years respectively. Fifty-two patients with either an unknown primary and metastatic disease prior to immunotherapy or mucous membrane primaries with metastatic disease prior to immunization were observed to have a 65% survival at four years while invasive ocular primary patients without metastatic disease prior to immunotherapy had a 70% four year survival in the 19 patients evaluable. The largest number of patients fall in the first two years of follow-up, therefore, the degree of confidence concerning the survival statistics for years 3 and 4 is broad at this point in time. Further follow-up with careful evaluation will be required before definition statements can be made and comparisons can be elicited. The overall survival statistics do, however, encourage continued evaluation of specific active immunotherapy for patients with invasive melanoma with both Stage I and Stage II disease.

MUCH OF THE HOST-TUMOR interaction in man must be studied in terms of membrane associated antigenic expression and the complexity of the various immune responses to these antigens. Normal human cells express both blood group antigens, and HLA-A, -B, -C and -D antigens. Tumor cells express these same blood group and HLA alloantigens but also express, in different concentrations, fetal antigens, differentiation antigens, and tumor associated antigens that are both cross-reactive and individually specific. The HLA antigens segregate independently from tumor associated antigens. In recent hybridoma studies[5] fused cells with deletion of the C6 chromosome do not express the serologically detectable HLA antigens but do express tumor associated antigens. The human histocompatibility Dr antigens have been reported to be important in both cell–cell interactions and for control of cell proliferation.[7] Their recent detection on melanoma cells[7] may indeed relate to the growth characteristics of these tumor cells and indicate their escape from immune destruction. The host responses to the membrane antigens of tumor cells involve lymphocytes, monocytes, and macrophages as well as other cell types. The immunity is not purely a cell mediated one for a variety of humoral immune responses have been described. Antimelanoma antibodies have been described in man[1,6] and their presence has been correlated with a favorable clinical course. The role of serum blocking factors, anti-idiotypic antibodies and immune complexes have been implicated in the abnormal immune regulation in the tumor-bearing host.

Transfer factor, immune RNA, and thymosin have had only ancedotal experience in clinical immunotherapy trials. Passive humoral and passive cellular attempts have had rather dramatic results in experimental animal models, but again clinical trials have been inconclusive. A number of nonspecific agents have been used as active immunopotentiators in clinical trials. The most popular ones have included levamisole, vaccinia, Corynebacterium Parvum and Bacillus Calmette-Guerin (BCG). Only limited success has been realized using these nonspecific agents. Specific active immunization has historically been our most efficient way of producing host immunity. For specific active immunization to be effective, the immunizing antigen should be accessible to host recog-

From the Departments of Surgery and Medicine, Duke University Medical Center and Veterans Administration Hospital, Durham, North Carolina

---

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

Reprint requests: H. F. Seigler, M.D., Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710.

Supported in part by CA 11265, General Clinical Cancer Research Center Grant, National Institutes of Health, and CA 20364, National Cancer Institute. Also supported by Program #821, Veterans Administration Hospital, Durham, North Carolina.

0003-4932/79/0900/0366 $00.85 © J. B. Lippincott Company

nition and possess a degree of immunogenicity. Host immune responsiveness must also be unimpaired. We have previously shown that human melanoma cells do indeed express tumor associated antigen(s) and this antigen(s) is immunogenic to most patients diagnosed with invasive melanomas. We report here our experience with specific active immunization in patients with Stage I and Stage II melanoma.

Materials and Methods

Melanoma Cells

The patients were actively immunized with approximately 2.5 × 10^7 x-irradiated (10,000r) neuraminidase treated melanoma cells, with BCG used as an adjuvant. Each immunization was spaced approximately four to six weeks apart, and appropriate clinical assessment was made to permit accurate staging of the disease. The tumor cells used in this study were established as primary tissue cultures. Both pigmented and nonpigmented melanoma cell lines were used for all experiments. The cultures were maintained in Eagle's Minimum Essential Medium plus 20% fetal calf serum. Each patient was immunized with only one tissue culture cell line. Both allogeneic and autochthonous immunizations were included.

Immunization Schedule

All patients were immunized subcutaneously with approximately 2.5 × 10^7 x-irradiated, neuraminidase treated melanoma cells, either allogeneic or autochthonous. The tumor vaccine was admixed with 0.1 cc Glaxo BCG for its adjuvant effect. No patient experienced any serious side effect to the vaccine and no local tumors at the injection site have been produced. Each immunization was scheduled at intervals of approximately six weeks.

Statistical Methods

Survival curves are presented as determined by both the direct method and the product-limit acturial method.[4] The latter method gives narrower 95% confidence intervals compared to the direct method. This effect is especially seen at the third and fourth year points for which relatively few patients are at risk because the majority of patients have entered the study within the past three years. Survival comparisons between subgroups were tested for significance by the Cox-Mantel test.[2] Continuity corrected Chi-square was used for comparison of discrete variables.

TABLE 1. *Distribution of Primary Melanoma*

Primary Site	No. Patients
Trunk	411 (42%)
Extremity	346 (35%)
Head and Neck	151 (15%)
Unk. Primary	46 (3%)
Eye	19 (2%)
Mucocutaneous	6 (1%)
	979

TABLE 2. *Melanoma Patients Receiving Specific Active Immunotherapy*

	Stage II	Stage I	Total
Clark III	54	297	351
Clark IV	75	170	245
Clark V	30	22	52
Unk. Primary			46
Mucocutaneous			6
Ocular			19
Evaluable			719
Clark I–II			109
Clark's Unk.	41	98	139
Incomplete Data			12
Total			979

Results

Nine hundred seventy-nine patients entered the study between 1972 and March, 1976. Incidence by site of the primary tumor given in Table 1 reflects the distribution observed in most studies of primary melanoma. Four hundred and eleven patients had truncal primary lesions while 346 originated on the extremities, 151 had a head and neck primary, and in 46 the primary site was unknown. Eye primaries and mucocutaneous lesions were observed in 19 and six patients respectively. Of the 979 patients, the 109 patients with Clarks Level I or II lesions did not receive immunotherapy. An additional 139 patients (41 stage I, 98 stage II) with known primary site were excluded from analysis because of undetermined Clark's Level. Twelve additional patients were not evaluable for survival because of incomplete information.

The remaining 719 patients were evaluable for survival. Of these, 351 had Clark's Level III lesions, 245 penetrated to Level IV and 52 were Level V lesions. Seventy-one patients could not be classified by Clark's Level because of an ocular (19), mucous membrane (6) or unknown primary (46) lesion.

Direct survival rates calculated through the fourth year from initial surgical treatment are presented in Figures 1–5. The vertical bars which enclose 95% confidence intervals broaden noticeably beyond the second year of follow-up, emphasizing that the great majority of patients have been at risk for less than four years. Actuarial survival estimates are given in Figures 6–9.

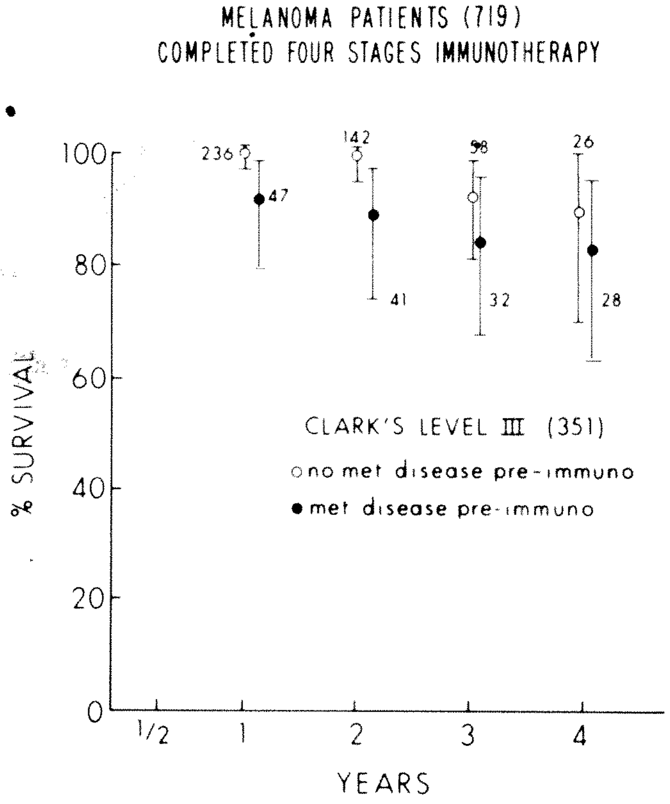


FIG. 1. Direct survival rates—Clark's Level III (351). Melanoma patients completing four stages of immunotherapy.

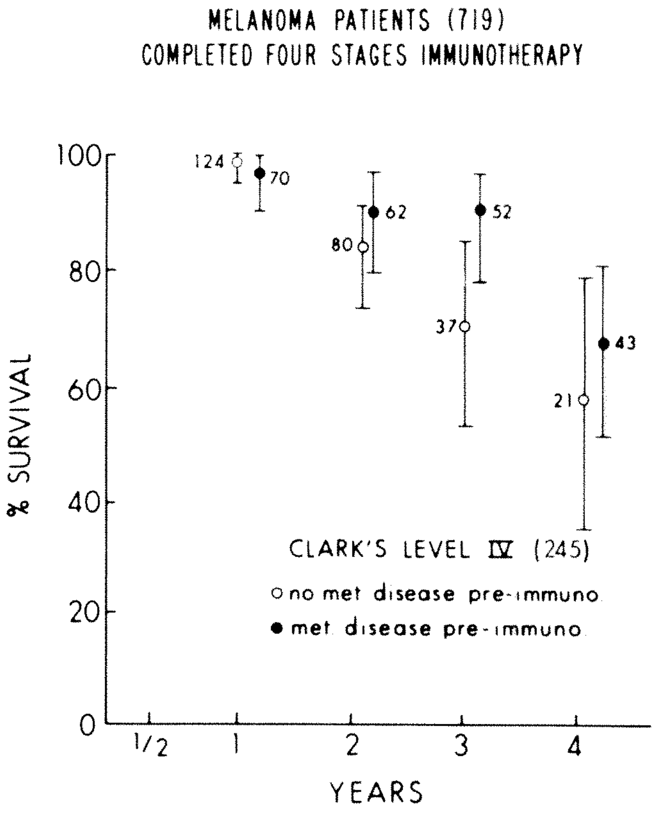


FIG. 2. Direct survival rates—Clark's Level IV (245). Melanoma patients completing four stages immunotherapy.

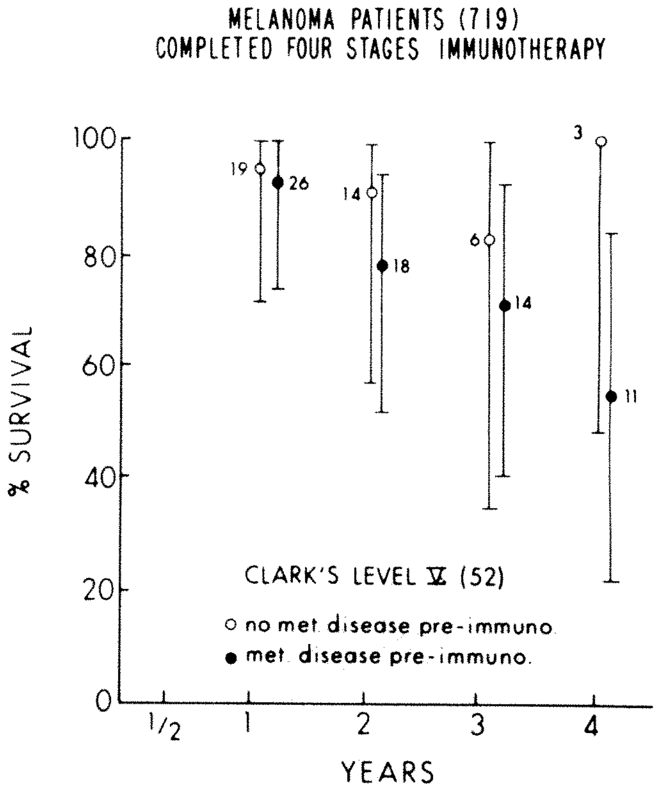


FIG. 3. Direct survival rates—Clark's Level V (52). Melanoma patients completing four stages immunotherapy.

At Clark's Level III, a significant difference was seen in survival time between Stage I and Stage II patients. No such difference was demonstrable in Level IV and V patients. In Stage II patients, no difference in prognosis by Clark's Level could be demonstrated, indicating that the attainment of metastasis became the overriding factor in prognosis irrespective of initial characteristics of the primary lesion.

No significant difference was seen in survival between patients with trunk and extremity primary lesions at Clark's Level III ($p = 0.11$) or Clark's Level IV ($p = 0.64$). The trend at Level III indicated slightly better survival for patients with extremity lesions, and at Level V, patients with extremity lesions survived significantly longer ($p = 0.02$). Grossly, women had longer survival than men, but once level of invasion and primary site had been accounted for, survival patterns for men and women were indistinguishable. (trunk, Level III, $p = 0.36$; extremity, Level III, $p = 0.23$; trunk, Level IV, $p = 0.30$). There was a preponderance of extremity lesions in women (M/F = 0.52) and trunk lesions in men (M/F = 1.65).

No prognostic value could be demonstrated for age once level and primary site were accounted for ($p = 0.39$).

Older patients tended to have more deeply invasive lesions. In patients younger than 60 years at diagnosis, 289 of 501 had Clark's Level III lesions (58%), while only 62 of 147 (42%) patients 60 and older had Level III lesions (chi-square = 11.0, p = 0.001).

Our total database consists of 1458 melanoma patients. Of these, 700 had extremity (259), trunk (348) or head and neck (93) lesions for which they might have had lymph node dissections at the time of initial surgery and for which information on lymph node surgery is complete. In 153, the clinical status of the lymph nodes was unknown; 45 of these patients had lymph node dissections. Fifty-eight patients had clinically positive nodes, of whom 48 had node dissections. Of the 489 clinical Stage I patients, 103 had elective lymph node dissections (21%), 30/245 (12%) with trunk lesions, 55/175 (31%) with extremity lesions, and 18/69 (26%) with head and neck lesions. Twenty-three of the 103 (22%) were histologically positive, 8 of 48 at Level III (17%), 10/43 at Level IV (23%) and 5/12 at Level V (42%). Seven deaths have occurred in these 103 patients, of which six were in the histologically positive group (chi-square = 17.4, p < 0.001).

Discussion

Only recently have immunologic techniques developed to the point that the role of the human immune response in the tumor-bearing patient can be reasonably evaluated. Although host immune responses to solid tumor cells occur in man, the immune phenomena detected *in vitro* do not always reflect *in vivo* events. The apparent inconsistencies emphasize the importance of careful analysis of immune responses to the tumor associated antigens. Melanoma patients obviously have encountered tumor associated antigen at some level prior to immunomanipulation and have not adequately eliminated these antigens presumably because some aberrant immunoregulatory mechanism has limited their immune response to the tumor. It has been well established in selected murine systems that T-lymphocytes immunized with syngeneic cells bearing nonself antigens ranging from haptens to minor histocompatibility differences to viral antigens, lyse target cells bearing the same antigen only if the target cells share histocompatibility antigens with the immunizing cells. This phenomena has been referred to as H-2 restriction. Recent evidence suggest that an analogous phenomena may occur in man.[3] The hypotheses concerning the relationship of nonself and histocompatibility antigens on target cell surfaces fall into two groups. One proposes that the two antigens are independent molecules recognized by two distinct T-cell receptors. The other proposes that two antigens occur in physical association on the cell surface and

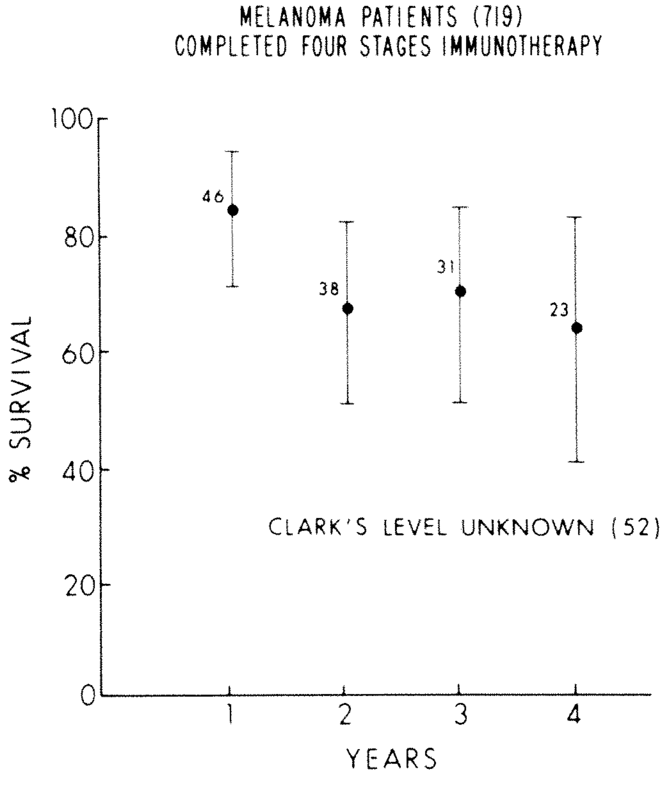


FIG. 4. Direct survival rates—Clark's Level unknown (52). Melanoma patients completing four stages immunotherapy.

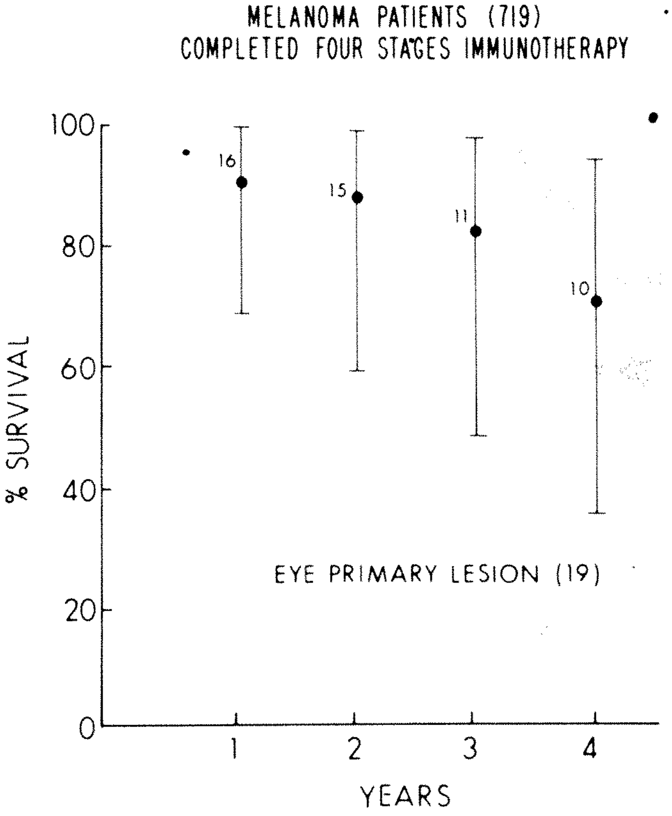


FIG. 5. Direct survival rates—eye primary lesion (19). Melanoma patients completing four stages immunotherapy.

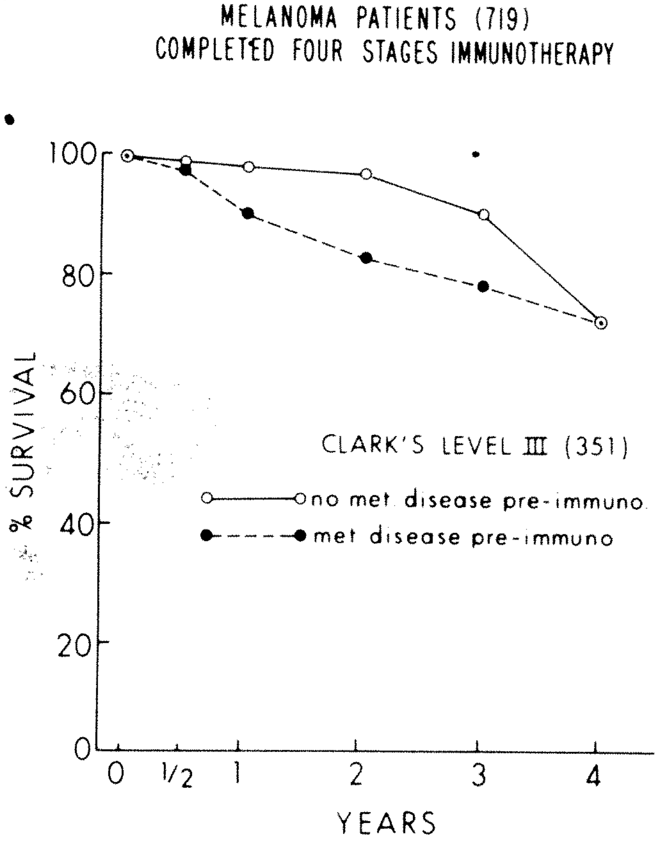


FIG. 6. Actuarial survival estimates—Clark's Level III (351). Melanoma patients completing four stages immunotherapy.

present to the T-cell a composite antigen. The latter hypothesis is supported by investigators who have shown that antigen specific for teratoma cells, endogenous viral antigens on chemically induced tumors, and Friend virus-determined cell surface molecules cocapped with H-2 antigens. In view of the availability of appropriate, well defined antisera and copious quantities of tumor tissue, we are now in an ideal situation to assess the association between melanoma and HLA antigens. These studies should provide considerable insight not only into immune recognition by human T-cells but also disparity of immune responses to tumor and normal alloantigens. In addition, studies concerning the density of tumor antigenic determinants on tumor cells must be completed in order to determine if antigen density determines qualitative and quantitative aspects of the patient's immune response to these tissues. Both primary and secondary cell-mediated cytotoxicity studies must be accomplished in patients that are to be considered for specific active immunotherapy. Additionally, levels of circulating lymphocytes capable of mediating antibody dependent cell-mediated cytotoxicity must also be evaluated. Suppression studies including evaluation of not only immune complexes and anti-idiotypic antibody but those concerning presumptive suppressor cell populations on mixed cell blastogenesis assays and cell mediated lysis assays require further characterization. Studies designed to characterize the activity of populations of cells fractionated into T- and B-cells and further fractionated T-cells into those bearing Fc receptors for IgG and those bearing Fc receptors for IgM can now technically be accomplished and may indeed lead to a better understanding of the host–tumor relationship.

The prognostic factors derived from this study reveal that by Clark's Level and stage of disease were the clinical factors which were of greatest importance. Stage of disease was the overriding factor in that, once nodal or distant metastasis was present, level of invasion gave no further prognostic information. There was an indication of shorter survival for patients with the more invasive trunk lesions although this was significant only for Level V patients. No difference was seen in the level of invasion between trunk and extremity primary lesions. Breslow's thickness measurement was available for only a small percentage of patients, so its contribution cannot be currently assessed. After accounting for Clark's Level, stage and primary site, sex and age were of no prognostic significance in these patients.

The role of lymphadenectomy in Stage I patients in this series cannot as yet be answered. The prevailing practice among surgeons referring melanoma patients to our institution for adjuvant treatment is to not

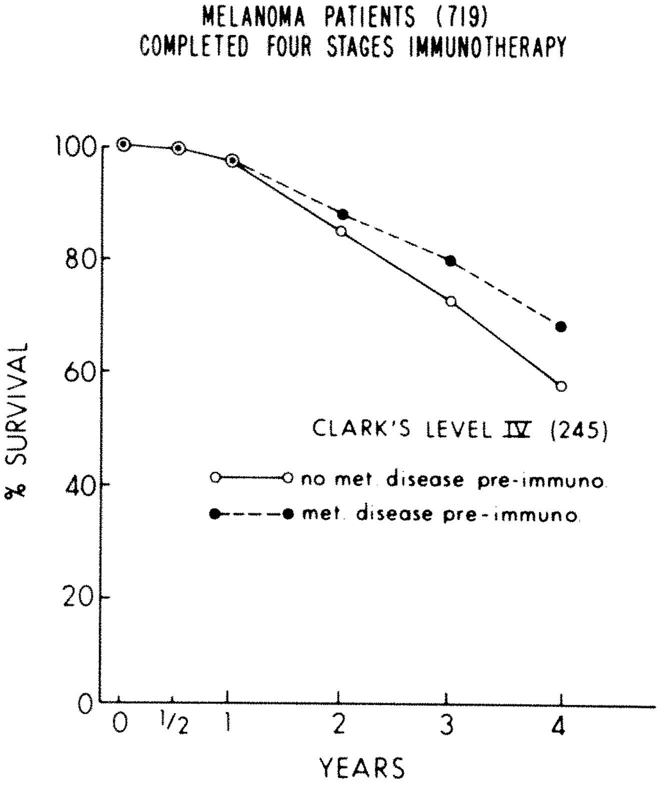


FIG. 7. Actuarial survival estimates—Clark's Level IV (245). Melanoma patients completing four stages immunotherapy.

perform lymphadenectomy in Stage I patients. Only 31% of patients with extremity lesions had dissections, and node dissections for trunk primaries were uncommon (12%). It will require longer follow-up to determine whether a beneficial effect of lymphadenectomy can be detected in this group of patients. The prognostic significance of histologically positive nodes in Stage I patients is already quite apparent, however, in that all but one of the seven deaths occurring to date in Stage I patients were in the small group of histologically positive patients.

Specific active immunization for production of an immune state has historically been effective for a variety of bacterial and viral diseases. If a similar course is to be realized for neoplastic diseases certain documentation of the tumor associated membrane antigen and its immunogenicity to the host must clearly be established. The complexities of the humoral and cellular response to these antigens requires further study and understanding. The patients presented in this preliminary report will remain under close follow-up with sequential monitoring of their immunological responses. Although early results are encouraging, the survival experience of the patients reported in this study must be considered tentative at this time because relatively few patients have been at risk for more than two years. Nevertheless, 95% confidence intervals at year one and two are quite narrow and the survival rates determined give a very accurate representation of experience in this group. Comparison of the one and two year survivals with reported experience in the literature by Clark's Level are encouraging, especially for the higher risk Levels IV and V. However, longer follow-up and careful evaluation will be required to assess with any certainty if the specific active immunotherapy regimen as presented will be of clinical significance.

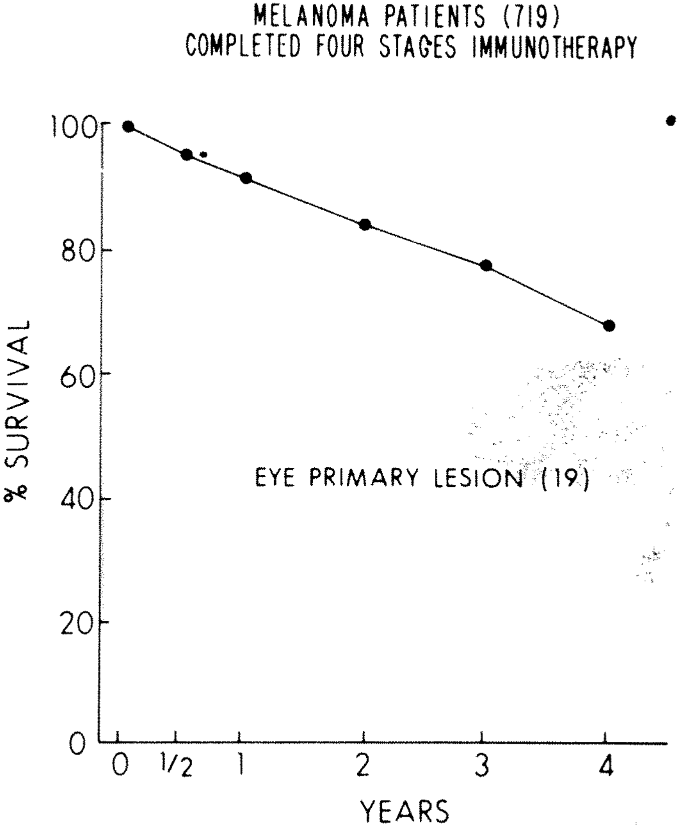


FIG. 9. Actuarial survival estimates—eye primary lesions (19). Melanoma patients completing four stages immunotherapy.

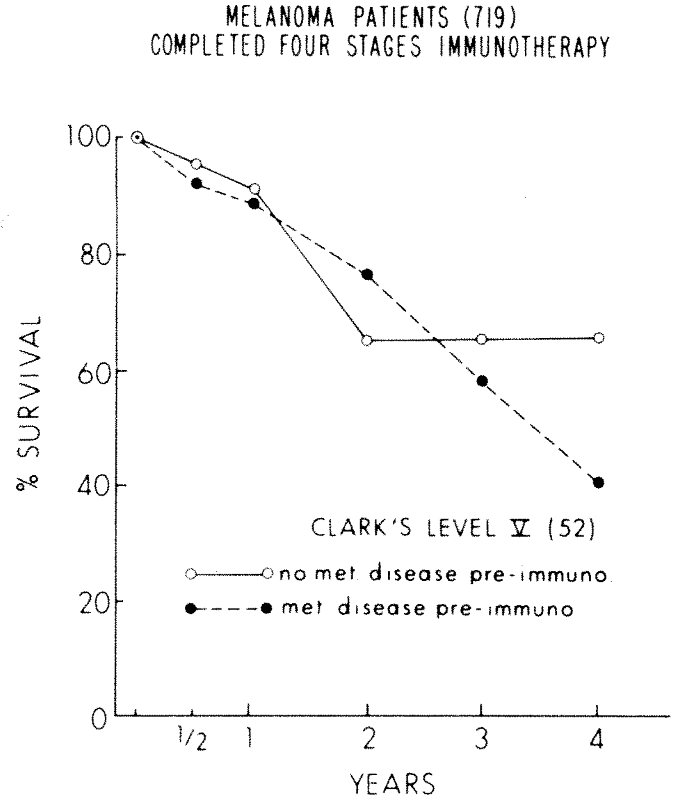


FIG. 8. Actuarial survival estimates—Clark's Level V (52). Melanoma patients completing four stages immunotherapy.

References

1. Bodurtha, A. J., Chee, D. O., Laucius, J. F., et al.: Clinical and Immunological Significance of Human Melanoma Cytotoxic Antibody. Cancer Res., 35:189, 1975.
2. Cox, D. R.: Regression Models and Life Tables. J. R. Stat. Soc. B, 34:187, 1972.
3. Gouling, E., Ternicjtelen, Bradley, B. A. and van Rood, J. J.: HLA Restriction of non-HLA-A, B, C and D Cell Mediated Lysis. Tissue Ant. 8:317, 1976.
4. Kaplan, E. L. and Meier, P.: Non-Parametric Estimation from Incomplete Observations. J. Am. Stat. Assoc., 53:457, 1958.
5. Koprowski, H., Steplewski, Z., Herlyn, D. and Herlyn, M.: Study of Antibodies Against Human Melanoma Produced by Somatic Cell Hybrids. Proc. Natl. Acad. Sci (USA), 75: 3405, 1978.
6. Lewis, M. G., McCloy, E. and Blake, J.: The Significance of Circulating Antibodies in the Localization of Human Malignant Melanoma. Br. J. Surg., 60:443, 1973.
7. Winchester, R. J., Ross, G. D., Jarowski, C. I., et al.: Expression of Ia-like Antigen Molecules on Human Granulocytes During Early Phases of Differentiation. Proc. Natl. Acad. Sci. (USA), 74:4012, 1977.

DISCUSSION

DR. LUCIUS D. HILL (Seattle, Washington): We have been applying immunotherapy in a somewhat different framework.

(slide) The Seattle group, over the past three years, has been using a double-blind randomized trial of immunotherapy as applied to resected cancer of the lung. This has included a three-arm study consisting of intrapleural BCG by the McNeely technique and BCG combined with levamisole in the second arm against a control arm. One hundred thirty-seven patients have been randomized to this trial over the past three years and the data would indicate at the present time that there has been an excellent correlation between the treatment arm and the conversion arm, or immunostimulation, as evidenced by PPD conversion.

It is interesting that the BCG-levamisole arm, which we had predicted initially would be the best arm because we were putting two immunostimulants or immunomodulator agents together, BCG for control of the intrathoracic spread of tumor and levamisole which theoretically should help control metastases, when compared to the placebo arm showed little difference. The BCG-levamisole has been disappointing, not only in terms of conversion from PPD negative to positive, but also as far as the outcome is concerned. The BCG alone arm has shown an excellent conversion, and in terms of survival rate the BCG arm, particularly in those patients who were PPD negative or anergic at the onset of the trial and who have converted to PPD positive, has shown a remarkable survival rate as compared with the control, whereas the BCG-levamisole arm has shown no statistical difference.

Without the control arm we would not have been able to detect these differences. As all of you know, in the past five years, particularly in cancer of the lung, with properly selected patients and improved therapy the survival rate for lung cancer, particularly in the Stage I cancers, has improved to the point that the Memorial Hospital Group has recently reported an 85% two year survival rate; our figures are coming out about the same.

I would like to ask the authors, therefore, is there a control arm in their study that was not evident in the abstract?

As far as the monoclonal specific antibody, or the antibody that they have detected as cytotoxic, we believe that this is one of the most important aims in the cancer field. As of this month the Hellstroms, who have been working with us on the lung cancer study and the melanoma study as well, have reported the isolation of a monoclonal specific antibody that is cytotoxic to the melanoma cell *in vitro*.

The thing that we need to know now is whether the presence of this antibody will help as far as outcome is concerned. I note in the abstract that the authors have said that they have detected this only in patients who do not have metastases. We need to know two things: Does this affect outcome? Are we going to be able to isolate the cell surface antigen that combines with this antibody?

DR. DONALD L. MORTON (Los Angeles, California): I thought I might share with you a brief synopsis of the present status of our studies of malignant melanoma.

(slide) Our initial observation, made some 12 years ago, suggested that persons with intracutaneous melanoma, when treated with intralesional BCG, often have regression of their disease and remain free of disease for many years.

These sorts of dramatic results in people with extensive disease led us to conduct a trial of adjuvant immunotherapy for patients with metastases to regional lymph nodes. Every patient who walked into the Clinic was offered immunotherapy. As you can see, the results for five years look good in that those patients who underwent operation and received immunotherapy had much better survival than those treated by operation alone. We were about to conclude that every patient with Stage II melanoma should receive immunotherapy. However, many of our colleagues suggested that there may have been some selection in this series; perhaps the patients that elected to have immunotherapy were different in some way from those treated by operation alone. These suggestions led to a properly randomized, controlled trial comparing three groups: patients who had operation only, patients who had BCG alone and patients who received BCG and tumor cell vaccine. I shall briefly summarize the results of the first two arms.

It was interesting to note that, although the original observation of the effect of immunotherapy was confirmed, the controls in the randomized trial did, in fact, do better than those in the nonrandomized trial, and the patients treated with BCG did about the same. Thus, the differences were not as impressive, but as you can see, patients who were treated with BCG survived significantly longer than the controls.

It is interesting that if one looks at recurrence at the present time—and we're four years into this trial—there is little difference in recurrence rate. Depending on time, there is only a 5–10% improvement in tumor-free survival rate. However, total survival rate is increased; the two-year survival rate for the controls is 60%, and for the BCG group, it is 81%. The four year rate is 50 and 58%. Thus, at four years into this randomized trial, differences in survival rate are not significant, but the two year rate is significant.

It is of interest that there was also a difference in site of first recurrence between the BCG group and the controls. The BCG group were more likely to have local or regional recurrences but the distribution of metastases to the brain and viscera were identical by the time of death.

In our series brain metastases continues to be a leading cause of death and treatment failure, and, thus far, our analyses of the data suggest that immunotherapy does not protect against brain metastasis. This is not an unexpected finding when we consider that the brain is an immunologically privileged site, but unless we can control the brain metastasis in some way, we may, in fact, allow our patients to win the first half of the ballgame, only to lose the series because of brain recurrence.

In closing, I would like to emphasize Dr. Hill's point. Dr. Seigler has ample patients for a prospective randomized trial, and I think that is the only way we can really arrive at a definitive conclusion for or against benefit from immunotherapy. As I recall, Dr. Das Gupta's data from Illinois showed that patients treated by operation alone—for example, Clark's Level III melanoma—had essentially 100% survival for those without metastatic disease at five years, and 95% survival in those with lymph node metastatic disease who have Level III primary disease. Such good results with operation alone make it difficult to evaluate the effect of adjuvant immunotherapy without a randomized trial.

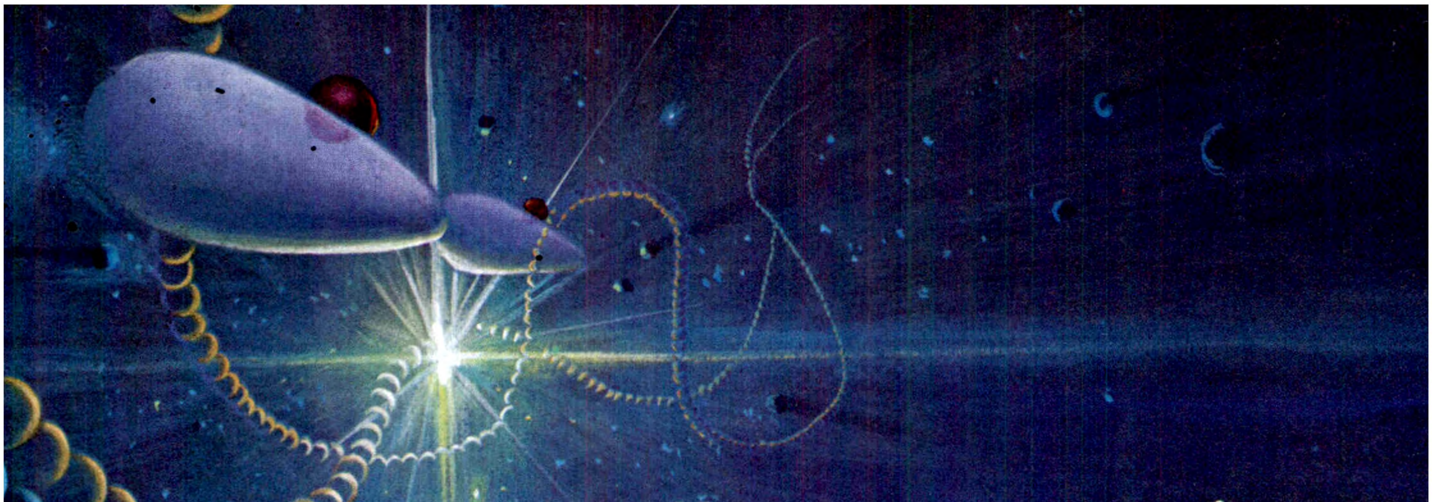
Therefore, I would like to ask the authors if such trials are contemplated.

DR. H. SEIGLER (Closing discussion): In answer to Dr. Hill first, we also have had a similar observation about the PPD conversion. We have found that PPD conversion is associated with specific immunization (BCG), and that you do not convert in and of itself other skin test unresponsiveness to a positive reaction.

In answer to Dr. Morton and to Dr. Hill about the controls: We do now have controls. Initially, we were trying to evaluate our ability to produce an antibody specifically against the tumor antigen, the patients that I presented today are controlled in two ways. Group one is allowed to go antibody-negative, while group two is maintained antibody-positive for their serum reactivity, we are trying to answer just the question that Dr. Hill posed, namely, what is the *in vivo* effectiveness of continuing circulating specific antibody against the target tumor cell?

The only group that we are prospectively controlling with no treatment is the Clark's Level IV patients, much for the reasons that Dr. Morton has mentioned.

in the progression of advanced breast cancer
your next therapeutic step may be the safest
TABLETS, 20 mg and 40 mg
MEGACE®
(MEGESTROL ACETATE)
antiestrogenic oral progestogen
For prescribing considerations, please see last page of this advertisement.



In advanced breast cancer, regression rates comparable to those usually obtained with chemotherapy or other endocrine therapies[1,2]

MEGACE was studied in 116 patients with advanced breast cancer; there was no selection of patients based on age, menopausal status, previous therapy, or physical state—near-terminal patients were not excluded.

Of the 95 evaluable patients,[*] MEGACE induced arrest or objective regression[†] in 47 (49.5%). An additional 12 patients (12.6%) had subjective improvement.[††][2]

MEGACE, rather than adding major adverse effects, may add subjective improvement

Patients who had had different degrees of anorexia and weight loss on entering clinical trials with MEGACE responded with increased appetite and weight gain, as well as an improved sense of well-being and amelioration of pain in the face of progressing disease.[1,2]

Serious adverse effects have not been reported in any study with MEGACE.[2] Unlike estrogens, androgens, and the antiestrogen, tamoxifen,[3-5] there have been no reports of "flares" in tumor pain, or of severe hypercalcemia in patients with bone metastases. Only a few occurrences of any adverse reactions to MEGACE have been reported. Minor or annoying side effects have been described as occurring in "...most" patients receiving tamoxifen.[6]

[*] Of the 116 patients, 21 were not evaluable due to inadequate follow-up.

[†] Definite decrease in size of half the lesions while other lesions remained static, or a decrease in half of non-osseous lesions with bone lesions static.

[††] Improved well-being, increased appetite, weight gain, and amelioration of pain in the face of progressing disease.

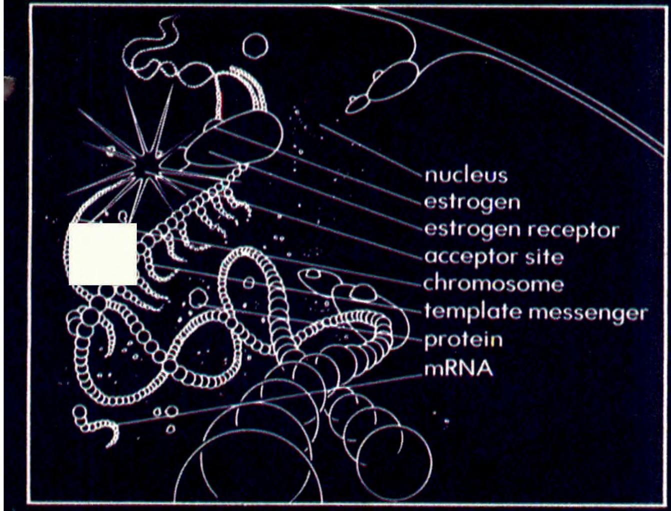
For prescribing considerations, please see last page of this advertisement.

MEGACE may help prolong the effectiveness of chemotherapy

In sequential, single, or combination therapy, a drug such as MEGACE—providing different biochemical mechanisms of action—may permit sequential use of chemotherapy by delaying or preventing acquisition of resistance by tumor cells to chemotherapeutic agents.[7] This is most important in continuing effective chemotherapy in responsive tumors.[4,6,8]

MEGACE may benefit patients at any sequence of therapy. Given after cytotoxic agent[illegible]n patients with widespread metastases, MEGACE may provide remission rates comparable to those with cytotoxic therapy...plus, a respite from toxicity and time for bone marrow to recover.[1,9]

MEGACE is the only oral progestogen indicated for palliative treatment of both advanced breast and endometrial cancer



Estrogen activation of cell begins with hormone's passage into cytoplasm. This occurs with all cells, but in estrogen-sensitive cells the hormone is "attracted" by a specific protein receptor. Binding of the hormone to the receptor protein permits both to pass through the nuclear membrane and attach nonspecifically to chromatin. Hormone-receptor complex moves to a specific effector site on the chromosome, where it triggers synthesis of messenger RNA corresponding to the gene at the site. Final step is migration of mRNA to cytoplasm, where it presides over protein synthesis.*

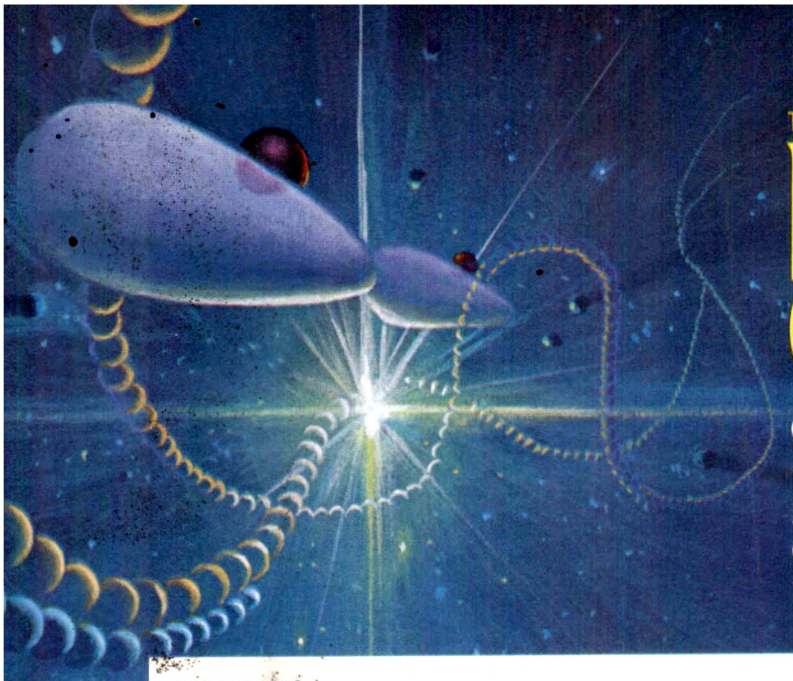
*Adapted from O'Malley.[10]

TABLETS, 20 mg and 40 mg

MEGACE®

(MEGESTROL ACETATE)

Mead Johnson PHARMACEUTICAL DIVISION



TABLETS, 20 mg and 40 mg

MEGACE®

(MEGESTROL ACETATE)

Oral endocrine therapy in advanced breast cancer

May benefit patients objectively and subjectively, with unsurpassed safety

REFERENCES:

1. Ansfield FJ, Davis HL Jr, Ramirez G, et al: Further clinical studies with megestrol acetate in advanced breast cancer. *Cancer* 38:53, 1976.
2. Data on file, Mead Johnson Pharmaceutical Division.
3. Carter SK: What you can do for your patients with breast cancer. *Res Staff Phy* 25:56–64, 1979.
4. Legha SW, Davis HL, Muggia FM: Hormonal therapy of breast cancer: new approaches and concepts. *Ann Intern Med* 88:69–77, 1978.
5. Minton MJ, Cantwell BMJ, Knight RK, et al: Safety of tamoxifen. *Lancet* 1:396–397, 1978.
6. Heuson J-C: Current overview of EORTC clinical trials with tamoxifen. *Cancer Treat Rep* 60:1463–1466, 1976.
7. Canellos GP, DeViat VT, Gold GL, et al: Combination chemotherapy for advanced breast cancer: response and effect on survival. *Ann Intern Med* 84:389–392, 1976.
8. Lippman ME, Allegra JC: Current concepts in cancer: receptors in breast cancer. *New Eng J Med* 2:930–933, 1978.
9. Ansfield FJ, Davis HL Jr, Ellerby RA, Ramirez G: A clinical trial of megestrol acetate in advanced breast cancer. *Cancer* 33:907–910, 1974.
10. O'Malley BW: Hormones, genes, and cancer. *Hosp Pract* 10:65, 1965.

WARNING

THE USE OF PROGESTATIONAL AGENTS DURING THE FIRST FOUR MONTHS OF PREGNANCY IS NOT RECOMMENDED

Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion or treat threatened abortion. There is no adequate evidence that such use is effective and there is evidence of potential harm to the fetus when such drugs are given during the first four months of pregnancy.

Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion. Therefore, the use of such drugs during the first four months of pregnancy is not recommended.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[1-5] One study[4] estimated a 4.7-fold increased risk of limb reduction defects in infants exposed *in utero* to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion).

Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 to 1,000.

If the patient is exposed to Megace during the first four months of pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus.

INDICATIONS

Megace (megestrol acetate) is indicated for the palliative treatment of advanced carcinoma of the breast or endometrium (i.e., recurrent, inoperable, or metastatic disease). It should not be used in lieu of currently accepted procedures such as surgery, radiation, etc.

CONTRAINDICATIONS

As a diagnostic test for pregnancy.

WARNINGS

Administration for up to 7 years of megestrol acetate to female dogs is associated with an increased incidence of both benign and malignant tumors of the breast. Comparable studies in rats and ongoing studies in monkeys are not associated with an increased incidence of tumors. The relationship of the dog tumors to humans is unknown but should be considered in assessing the benefit-to-risk ratio when prescribing Megace and in surveillance of patients on therapy.

The use of Megace (megestrol acetate) in other types of neoplastic disease is not recommended.

PRECAUTIONS

There are no specific precautions identified for the use of Megace (megestrol acetate) when used as recommended. Close, customary surveillance is indicated for any patient being treated for recurrent or metastatic cancer. Use with caution in patients with a history of thrombophlebitis.

ADVERSE REACTIONS

No untoward effects have been ascribed to Megace therapy. Reports have been received of patients developing carpal tunnel syndrome, deep vein thrombophlebitis and alopecia while taking megestrol acetate.

OVERDOSAGE

No serious side effects have resulted from studies involving Megace (megestrol acetate) administered in dosages as high as 800 mg/day.

DOSAGE AND ADMINISTRATION

Breast cancer: 160 mg/day (40 q.i.d.).

Endometrial carcinoma: 40–320 mg/day in divided doses.

At least two months of continuous treatment is considered an adequate period for determining the efficacy of Megace (megestrol acetate).

HOW SUPPLIED

Megace® is available as light blue, scored tablets containing 20 mg or 40 mg megestrol acetate in bottles of 100 tablets each.

NDC 0087-0595-01, 20 mg tablet	Bottles of 100
NDC 0087-0596-41, 40 mg tablet	Bottles of 100

References:

1. Gal I, Kirman B, Stern J: Hormonal pregnancy tests and congenital malformation. *Nature* 216:83, 1967.
2. Levy EP, Cohen A, Fraser FC: Hormone treatment during pregnancy and congenital heart defects. *Lancet* 1:611, 1973.
3. Nora J, Nora A: Birth defects and oral contraceptives. *Lancet* 1:941, 1973.
4. Janerich DT, Piper JM, Glebatis DM: Oral contraceptives and congenital limb-reduction defects. *New Eng J Med* 291:697, 1974.
5. Heinonen OP, Slone D, Monson RR, et al: Cardiovascular birth defects and antenatal exposure to female sex hormones. *New Eng J Med* 296:67, 1977.

Mead Johnson PHARMACEUTICAL DIVISION

© 1979 Mead Johnson & Company • Evansville, Indiana 47721 U.S.A. MJL 9-4440

There are more reasons for drinking Carnation Instant Breakfast than you can shake a stick at.

Just one packet mixed with milk contains 15 gm. of protein. It supplies 25% of the RDA of vitamins and minerals, too. All that good liquid nourishment in just 280 quick, convenient Calories. Lots of good reasons for your patients to drink Carnation Instant Breakfast. Milk contributes substantial nutrition, too. (Just read the label.)

To help you use it more effectively in your practice we've developed free diet plans with Carnation Instant Breakfast. They're very flexible, and supply adequate quantities of essential nutrients in each day's menu.

Each booklet has 12 identical, tear-out patient plans with general instructions, a basic meal plan and sample menu. There's even a column for your special notes.

By the way, Carnation Instant Breakfast tastes like a rich, creamy milkshake. Be sure to try it when you get your professional sample. It's also available in crunchy bars.

Check the FREE diet plans you'd like.

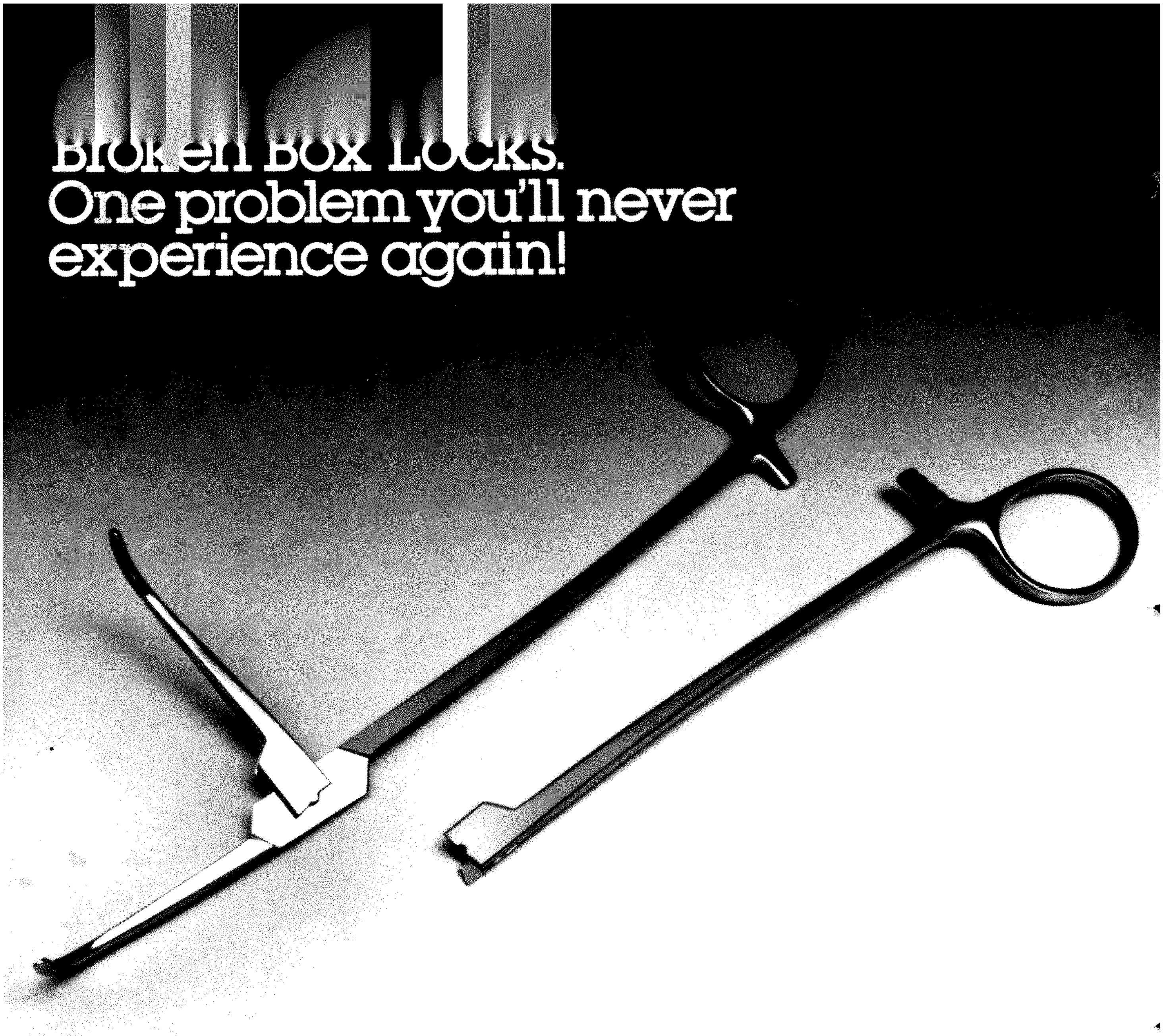
☐ Residue Controlled.
☐ Purine Restricted.
☐ High Protein.
☐ Liberal Bland.

NAME ______________________

ADDRESS ______________________

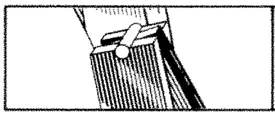
CITY ______________________

STATE ______________ ZIP ______________

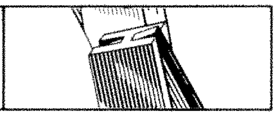


Broken Box Locks.
One problem you'll never experience again!

You've had vascular clamps break in surgery. It'll never happen again. Pilling box locks are virtually indestructible — they will not break! Our Life-Lok® box lock construction protects your patient and assures confidence in your clamps.



Non-Pilling Riveted Pin Construction. Failure prone. Box lock can break.



Life-Lok® Construction. No riveted pin. Box lock won't break.

Other clamps may look alike, but none can give you the same performance. Two U.S. patents protect Pilling clamps against duplication.

Pilling has 350 different vascular clamps — *more than any other company* — matching the anatomical considerations for almost every surgical approach you use.

For aortic and peripheral vascular occlusion, you get complete vessel control efficiently and safely.

Pilling Life-Lok® construction carries U.S. Patent numbers 3911766 and 3952749.

Non-traumatic Atraugrip® jaw serrations — patented by Pilling and now widely imitated, control vessels without crushing. You get complete vessel occlusion *with intimal protection.*

We want to send you full specifications on the clamps that can enhance your surgical technique. *Call us direct.* We'll send you our 240 page catalog showing how Pilling clamps can do more for you in the operating room than any other clamps.

Call toll free Ask for Pilling's latest catalog of vascular, thoracic, and cardiac instruments.

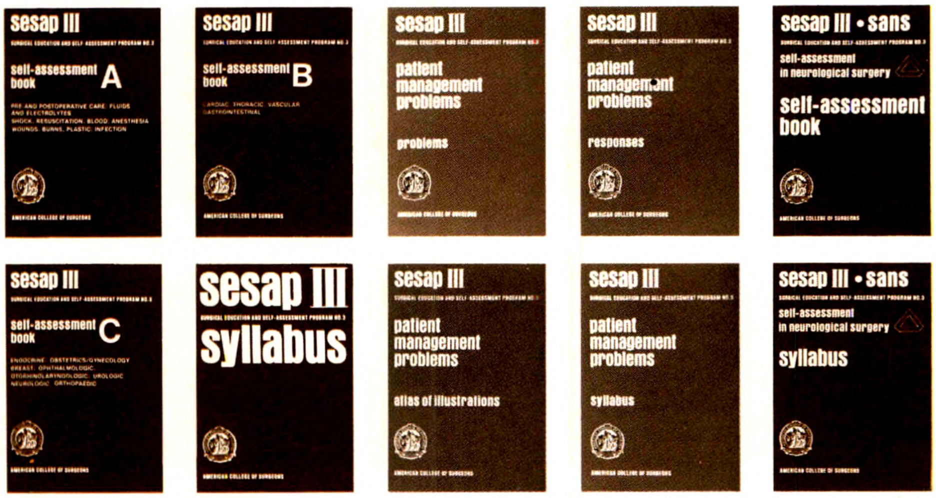
800-523-6507

215-643-2600 in Pennsylvania or write
Mr. William Taylor at the address below.

NARCO PILLING
A Division of Narco Scientific
Delaware Drive
Fort Washington, PA 19034, U.S.A.

All-new . . . improved . . . expanded

sesap III



The 3rd Surgical Education and Self-Assessment Program of the American College of Surgeons

NOW OPEN FOR ENROLLMENT AND COMPUTER-SCORING

- Three self-assessment books with 750 clinically oriented multiple-choice items
- SESAP III Syllabus with detailed critique of each item
- 15 Patient Management Problems (PMP) with Atlas of Illustrations
- PMP Syllabus with comprehensive discussion of each PMP
- Computer-generated individual critiques of performance
- Certificate of participation

Credit Hours in Category I for Participation in Computer-Scoring

155 credit hours in Category I toward the Physician's Recognition Award of the American Medical Association for completion of SESAP III self-assessment and participation in computer-scoring

For Neurosurgeons

Optional combination of SESAP III with a Self-Assessment in Neurological Surgery (SESAP III-SANS) containing:

- SESAP III material, *plus*
- SANS self-assessment book with 200 multiple-choice items
- SANS Syllabus with critique of each item

185 credit hours in Category I toward the Physician's Recognition Award of the AMA for completion of optional SESAP III-SANS combination and participation in computer-scoring

DEADLINE FOR PARTICIPATION IN COMPUTER-SCORING FEBRUARY 29, 1980

IF YOU HAVE NOT RECEIVED YOUR SESAP III PROSPECTUS IN THE MAIL, ASK FOR COMPLETE DETAILS NOW! CLIP AND MAIL THIS COUPON!

SESAP and Recertification

The College and the American Board of Surgery have agreed to correlate SESAP with the Board's recertification process. Questions formulated by the Board for the examination portion of its recertification process will be based on the clinical and other subjects addressed by SESAP.

YES, I wish to learn more about **SESAP III** and **SESAP III-SANS.** Please send me, without cost or obligation, a Prospectus explaining in detail the third Surgical Education and Self-Assessment Program of the American College of Surgeons.

NAME (PLEASE PRINT OR TYPE)

ADDRESS

CITY AND STATE ZIP AN 9/79

sesap

American College of Surgeons
55 EAST ERIE STREET
CHICAGO, ILLINOIS 60611

THE CEPHALOSPORIN COST CONTAINMENT CALCULATOR.

"The determination as to which product to select has turned out to be almost entirely, if not entirely, on the basis of cost. Cephalothin and cephapirin...can be considered identical in terms of pharmacokinetics, therapeutic efficacy and toxicology. Also, in terms of therapeutic efficacy and toxicology, these two compounds are similar to cefazolin."*

—Richard Quintiliani, M.D.
Director, Division of Infectious Diseases
Hartford Hospital[1]

*Cephapirin, cephalothin and cefazolin are not chemically or generically equivalent and any statements made comparing these products are valid only when considering mutually approved indications.

Cephalosporins account for 39% of all hospital parenteral antibiotic purchases. That's a lot of cost to contain. But the potential for savings is great.

And, the only machine you'll ever need to calculate maximum cephalosporin savings is already on your desk.

For specific details on how Cefadyl can save money for your institution, just pick up your telephone and dial one of the toll-free numbers listed below.

Everyone talks about hospital cost containment. But Bristol Laboratories has a cephalosporin price worth talking about!

Call the Cefadyl Cost Containment Hotline today—

In the Continental U.S., call toll-free

800-448-5779

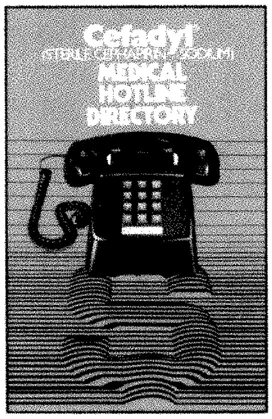
(In New York State, call toll-free 800-962-5746)

Cefadyl®
(STERILE CEPHAPIRIN SODIUM)
can save money!

SEE NEXT PAGE FOR PRESCRIBING INFORMATION

Connect yourself to the Cefadyl® (STERILE CEPHAPIRIN SODIUM) MEDICAL HOTLINE–FREE!

The Cefadyl Medical Hotline Directory lists all the government agencies and private institutions that affect the practice of medicine in America today. And, for most listings, the Directory includes names and numbers of the key individuals, not just a general switchboard.



To obtain your free copy of the Cefadyl Medical Hotline Directory, just call toll-free
800-448-5779
in Continental U.S.
(New York State residents call toll-free
800-962-5746).

Cefadyl® (STERILE CEPHAPIRIN SODIUM) can save money!

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CEFADYL®
(sterile cephapirin sodium)
(7) Cefadyl 3/6/78

For complete prescribing information, please consult the Official Package Circular.

Contraindications

Cefadyl (sterile cephapirin sodium) is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

Warnings

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs,should receive antibiotics cautiously and then only when absolutely necessary. No exceptions should be made with regard to Cefadyl.

If an allergic or anaphylactic reaction should occur, discontinue Cefadyl and institute appropriate treatment.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions

The renal status of the patients should be determined prior to and during Cefadyl therapy, since in patients with impaired renal function, a reduced dose may be appropriate.

Prolonged use of Cefadyl may result in the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken. With high urine concentrations of cephapirin, false-positive glucose reactions may occur if Clinitest, Benedict's Solution or Fehling's Solution are used. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Tes-Tape) be used.

Adverse Reactions

Hypersensitivity — Cephalosporins were reported to produce the following reactions: maculopapular rash, urticaria, reactions resembling serum sickness, and anaphylaxis. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—During large-scale clinical trials, rare instances of neutropenia, leukopenia, anemia were reported. Some individuals, particularly those with azotemia, have developed positive direct Coombs' test during therapy with other cephalosporins.

Liver—Elevations in SGPT or SGOT, alkaline phosphatase, and bilirubin have been reported.

Kidney—Rises in BUN have been observed; their frequency increases in patients over 50 years old.

How Supplied

Cefadyl (sterile cephapirin sodium) for I.M. or I.V. Injection. Cephapirin sodium equivalent to 1 Gm., 2 Gm., 4 Gm., or 20 Gm. cephapirin. For information on package sizes available, refer to the current price schedule.

1. Quintiliani R: The Cephalosporins: An Overview, film, (Feb) 1979.

BRISTOL®
©1979 BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, N.Y. 13201

B[illegible]us[illegible] you need to know which patient is at risk of postoperative thrombosis...

ORTHO* Chromogenic Antithrombin III Assay

Available now for incorporation into your routine screening procedures, as:

- A presurgical screen for levels of Antithrombin III
- An adjunct to heparin monitoring procedures

ORTHO DIAGNOSTICS INC.
Raritan, New Jersey 08869

*Trademark © O.D. 1979

I am interested in Antithrombin III (AT III). Please send me:

☐ Selected reprints on the diagnostic utility of ORTHO* Chromogenic Antithrombin III Assay

☐ An informative brochure on AT III as an inhibitor and the principles of the ORTHO Chromogenic AT III Assay

Name ______

Address ______

City ______ State ______ Zip ______

Your specialty ______

Who, in your hospital, establishes routine presurgical screening procedures ______

______

*Trademark

ORTHO

A distinguished surgical series

COMPREHENSIVE MANUALS OF SURGICAL SPECIALITIES

Edited by **Richard H. Egdahl,** Boston University Medical Center

This outstanding series of surgical manuals emphasizes large, detailed, full-color illustrations, most depicted from the perspective of the operating physician, to demonstrate the integral steps in surgical procedures. Each book focuses on a specific region or topic and describes surgical anatomy, physiology, pathology, diagnosis and operative treatment. Postoperative and complication management are studied in depth as well.

All the volumes in the series contain 200-300 clearly defined and annotated illustrations and are organized and indexed to permit easy access to information.

Published Volumes

Manual of Gynecologic Surgery
By **Byron J. Masterson**
1979/272 pp./197 illus./Cloth $79.80
ISBN 0-387-90372-0

Manual of Surgery of the Gallbladder, Bile Ducts and Exocrine Pancreas
By **Robert E. Hermann**
1979/xiv, 306 pp./320 illus.
(196 in full color)/Cloth $84.50
ISBN 0-387-90351-8

Manual of Burns
By **W. Scott McDougal, C. Lawrence Slade** and **Basil A. Pruitt, Jr.**
1978/x, 165 pp./214 color illus./Cloth $62.50
ISBN 0-387-90319-4

Manual of Endocrine Surgery
By **Anthony J. Edis, Luis A. Ayala** and **Richard H. Egdahl**
1975/xiii, 274 pp./266 illus.
242 color plates/Cloth $44.30
ISBN 0-387-07064-8

Forthcoming Volumes

Manual of Lower Gastrointestinal Surgery
By **Claude E. Welch, Leslie W. Ottinger** and **John P. Welch**

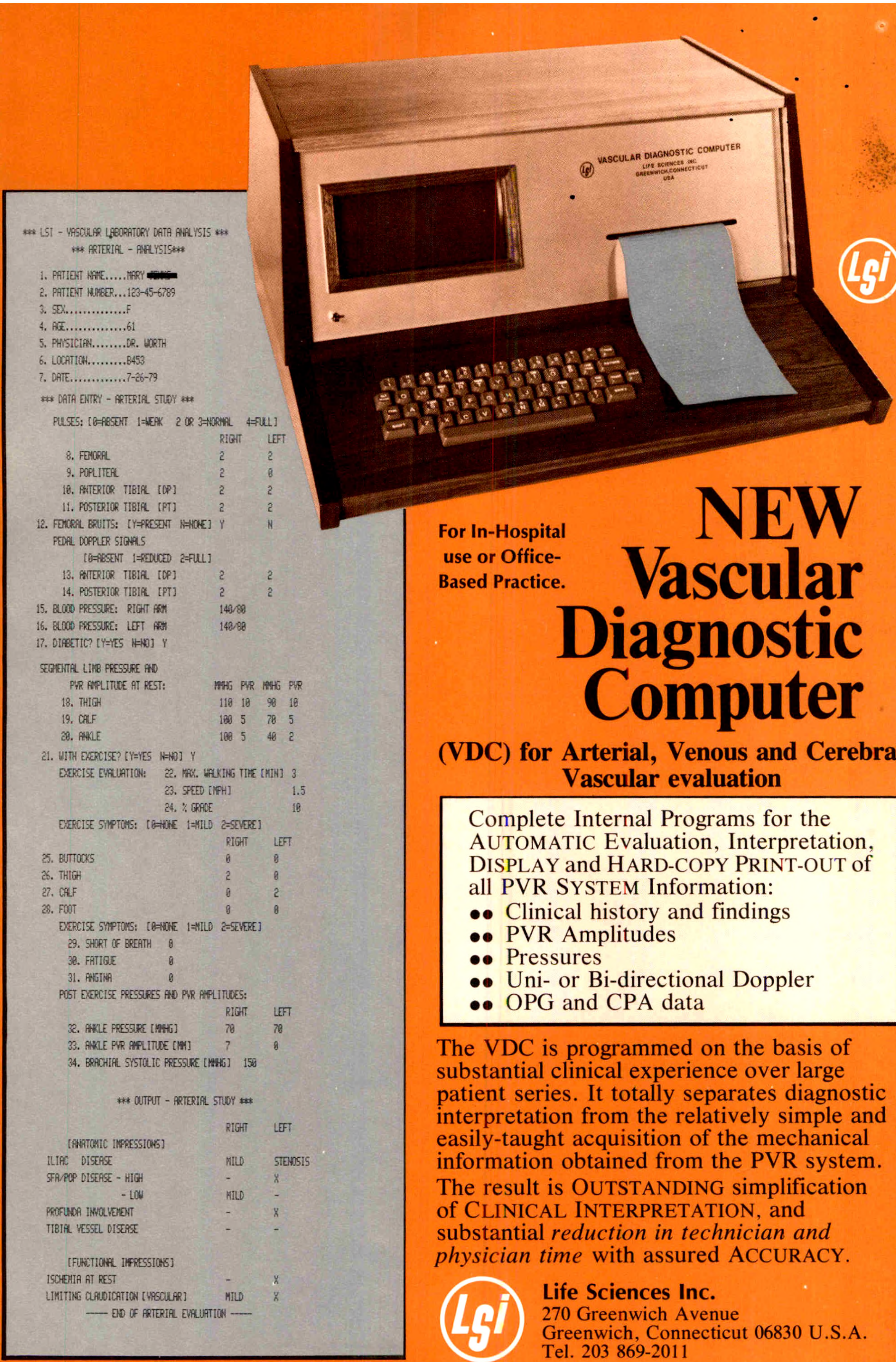
Manual of Urologic Surgery
By **Abraham T.K. Cockett** and **Ken Koshiba**

Manual of Vascular Surgery
Volumes I and II
By **E.J. Wylie, R.J. Stoney** and **W.K. Ehrenfeld**

Manual of Cardiac Surgery
Volumes I and II
By **Bradley Harlan** and **Albert Starr**

Prices subject to change without notice.

Springer-Verlag New York Inc.
Dept. S132
175 Fifth Avenue
New York, New York 10010



```
*** LSI - VASCULAR LABORATORY DATA ANALYSIS ***
        *** ARTERIAL - ANALYSIS***

  1. PATIENT NAME.....MARY [redacted]
  2. PATIENT NUMBER...123-45-6789
  3. SEX.............F
  4. AGE.............61
  5. PHYSICIAN........DR. WORTH
  6. LOCATION.........B453
  7. DATE............7-26-79
  *** DATA ENTRY - ARTERIAL STUDY ***
    PULSES: [0=ABSENT  1=WEAK   2 OR 3=NORMAL   4=FULL]
                                        RIGHT     LEFT
       8. FEMORAL                       2         2
       9. POPLITEAL                     2         0
      10. ANTERIOR  TIBIAL  [DP]        2         2
      11. POSTERIOR TIBIAL  [PT]        2         2
 12. FEMORAL BRUITS:  [Y=PRESENT  N=NONE] Y       N
    PEDAL DOPPLER SIGNALS
          [0=ABSENT  1=REDUCED  2=FULL]
      13. ANTERIOR  TIBIAL  [DP]        2         2
      14. POSTERIOR TIBIAL  [PT]        2         2
 15. BLOOD PRESSURE:  RIGHT ARM         140/80
 16. BLOOD PRESSURE:  LEFT  ARM         140/80
 17. DIABETIC? [Y=YES  N=NO]  Y

  SEGMENTAL LIMB PRESSURE AND
       PVR AMPLITUDE AT REST:          MMHG  PVR  MMHG  PVR
     18. THIGH                         110   10   90    10
     19. CALF                          100   5    70    5
     20. ANKLE                         100   5    40    2
  21. WITH EXERCISE? [Y=YES  N=NO]  Y
     EXERCISE EVALUATION:    22. MAX. WALKING TIME [MIN]  3
                             23. SPEED [MPH]              1.5
                             24. % GRADE                  10
     EXERCISE SYMPTOMS:  [0=NONE  1=MILD  2=SEVERE]
                                        RIGHT     LEFT
  25. BUTTOCKS                          0         0
  26. THIGH                             2         0
  27. CALF                              0         2
  28. FOOT                              0         0
     EXERCISE SYMPTOMS:  [0=NONE  1=MILD  2=SEVERE]
       29. SHORT OF BREATH    0
       30. FATIGUE            0
       31. ANGINA             0
     POST EXERCISE PRESSURES AND PVR AMPLITUDES:
                                        RIGHT     LEFT
       32. ANKLE PRESSURE [MMHG]        70        70
       33. ANKLE PVR AMPLITUDE [MM]     7         0
       34. BRACHIAL SYSTOLIC PRESSURE [MMHG]   150

              *** OUTPUT - ARTERIAL STUDY ***

                                        RIGHT     LEFT
      [ANATOMIC IMPRESSIONS]
  ILIAC   DISEASE                       MILD      STENOSIS
  SFA/POP DISEASE - HIGH                -         X
                  - LOW                 MILD      -
  PROFUNDA INVOLVEMENT                  -         X
  TIBIAL VESSEL DISEASE                 -         -

      [FUNCTIONAL IMPRESSIONS]
  ISCHEMIA AT REST                      -         X
  LIMITING CLAUDICATION [VASCULAR]      MILD      X
           ---- END OF ARTERIAL EVALUATION ----
```

For In-Hospital use or Office-Based Practice.

NEW Vascular Diagnostic Computer

(VDC) for Arterial, Venous and Cerebral Vascular evaluation

Complete Internal Programs for the AUTOMATIC Evaluation, Interpretation, DISPLAY and HARD-COPY PRINT-OUT of all PVR SYSTEM Information:
- Clinical history and findings
- PVR Amplitudes
- Pressures
- Uni- or Bi-directional Doppler
- OPG and CPA data

The VDC is programmed on the basis of substantial clinical experience over large patient series. It totally separates diagnostic interpretation from the relatively simple and easily-taught acquisition of the mechanical information obtained from the PVR system.

The result is OUTSTANDING simplification of CLINICAL INTERPRETATION, and substantial *reduction in technician and physician time* with assured ACCURACY.

Life Sciences Inc.
270 Greenwich Avenue
Greenwich, Connecticut 06830 U.S.A.
Tel. 203 869-2011

What cancer can't kill:

HOPE. LOVE. COMPASSION. DIGNITY. TENDERNESS. UNDERSTANDING.

Because now there's a book of sound advice for everyone whose loved one has cancer.

How do you cope with cancer when someone you care for is the victim? How can you deal with the anger, fear and anxiety? Until now, the answer was a vague one. Today, however, there is a book—by an expert—that is a straightforward, wise, human discussion that can truly help you. It avoids both extreme anxiety and passive acceptance, looking for a middle way of reacting that may actually improve the chances of a cure.

Doing for yourself—with the help of an expert.

Out of the experience of thousands of patients, Dr. Cantor talks about every emotional consequence of the cancer experience. He discusses such vital emotional issues as faith in the physician; fear of abandonment; the process of restitution; the failure of treatment; how different types of marriages and family relationships are likely to respond; handling depression, and much more. Just about everything you could ever want to know, every piece of advice you could ever need, is contained in *And A Time to Live.*

If you need help getting through your experience with cancer in someone you love, you need this book. It will help you have the kind of hope you never thought possible.

"A fine and useful book, unusual in its scope, insight, and compassion."
—ALLEN B. WHEELIS, MD., author of *The Seeker*

"An extraordinarily fine book . . . It is full of vitally important information and wise counsel for people who have cancer and for all who relate to them as professionals, family members, or friends."
—NEVITT SANFORD, author of *The Authoritarian Personality*

AND A TIME TO LIVE
Toward Emotional Well-Being During the Crisis of Cancer
by Dr. Robert Chernin Cantor
$10.95

At your bookstore, or:

HARPER & ROW, Publishers
Attn: R. Brengel
10 East 53rd Street
New York, N.Y. 10022

Please send me ________ copies of *And A Time to Live* @ **$10.95** per copy plus 75¢ for postage and handling. If not satisfied, I may return the book(s) within 10 days for a full refund. I enclose ☐ check ☐ money order in the amount of $________ total. (Please add applicable sales tax.)

Name ____________________

Address ____________________

City ____________ State ______ Zip ______

M.V.I.® (Multi-Vitamin Infusion)

Each 10 cc. ampul† or 5 cc. Concentrate vial†† provides:

Ascorbic acid (C)	500 mg.
Vitamin A*	10,000 I.U.
Vitamin D* (ergocalciferol)	1,000 I.U.
Thiamine HCl (B_1)	50 mg.
Riboflavin (B_2)**	10 mg.
Pyridoxine HCl (B_6)	15 mg.
Niacinamide	100 mg.
Dexpanthenol	25 mg.
Vitamin E* (dl-alpha tocopheryl acetate)	5 I.U.

†With sorethytan laurate 1%, sodium hydroxide 1%, butylated hydroxytoluene 0.003%, butylated hydroxyanisole 0.0008%; and gentisic acid ethanolamide 2% as preservative.

††With propylene glycol 30% and gentisic acid ethanolamide 2% as stabilizers and preservatives, sodium hydroxide for pH adjustment, sorethytan laurate 1.6%, butylated hydroxytoluene 0.006%, butylated hydroxyanisole 0.0015%.

*Oil-soluble vitamins A, D and E water solubilized with sorethytan laurate.

**In Concentrate as riboflavin-5-phosphate.

BRIEF SUMMARY

INDICATIONS: *in emergency feedings*– Surgery, extensive burns, fractures and other trauma, severe infectious diseases, comatose states, etc. may provoke a "stress" situation with profound alterations in the body's metabolic demands and consequent tissue depletion of nutrients. As a result, wound healing may be impaired, enzyme activity disturbed, hematopoietic tissues affected; hypoproteinemia and edema may appear; convalescence is thus prolonged.

In such patients M.V.I. (administered in intravenous fluids under proper dilution) contributes optimum vitamin intake toward maintaining the body's normal resistance and repair processes.

DIRECTIONS FOR USE: M.V.I. is ready for immediate use when added to intravenous infusion fluids.

For intravenous feeding, one daily dose of 10 cc. of M.V.I. or 5 cc. of M.V.I. Concentrate added directly to not less than 500 cc., preferably 1,000 cc., of intravenous dextrose, saline or similar infusion solutions...plasma, protein hydrolysates, etc.

PRECAUTION: Allergic reaction has been known to occur following intravenous administration of solutions containing thiamine.

CAUTION: Not to be given as a direct undiluted intravenous injection as it may give rise to dizziness, faintness, etc.

THERAPEUTIC NOTE: Intravenous use should be discontinued as early as practical in favor of an intramuscular or oral vitamin preparation, if deemed advisable.

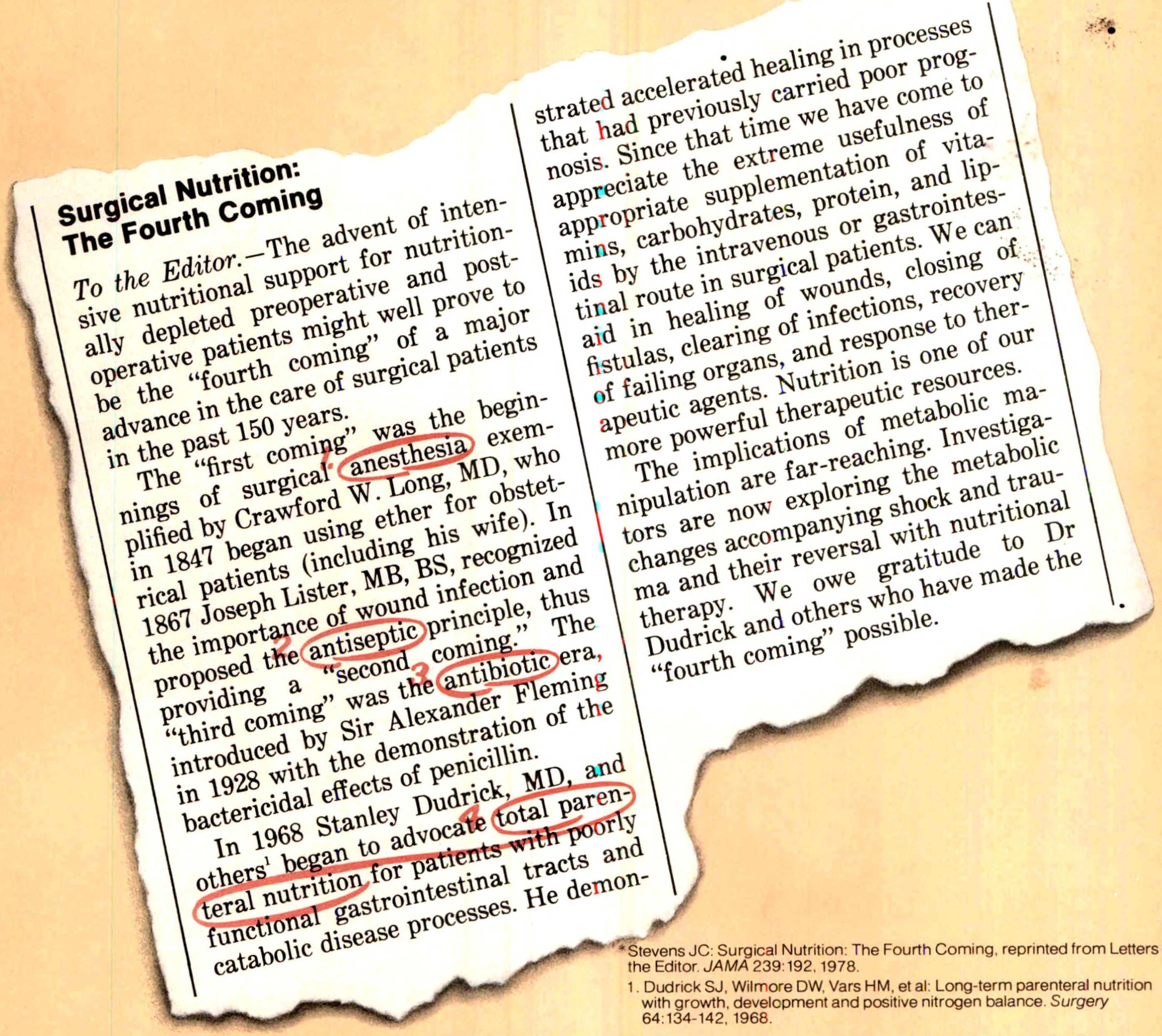
HOW SUPPLIED: M.V.I.–10 cc. ampuls, boxes of 25 and 100 (NSN 6505-00-455-9955/NSN 6505-00-424-9808A).

M.V.I. CONCENTRATE–5 cc. vials, boxes of 25. Available in 100s only (NSN 6505-00-212-6156A).

USV LABORATORIES
USV Laboratories, Division
USV Pharmaceutical Corp.
Tuckahoe, New York 10707

Four Discoveries That Changed Medical History

Reprinted from Letters to the Editor, JAMA.*



Surgical Nutrition: The Fourth Coming

To the Editor.—The advent of intensive nutritional support for nutritionally depleted preoperative and postoperative patients might well prove to be the "fourth coming" of a major advance in the care of surgical patients in the past 150 years.

The "first coming" was the beginnings of surgical 1 anesthesia exemplified by Crawford W. Long, MD, who in 1847 began using ether for obstetrical patients (including his wife). In 1867 Joseph Lister, MB, BS, recognized the importance of wound infection and proposed the 2 antiseptic principle, thus providing a "second coming." The "third coming" was the 3 antibiotic era, introduced by Sir Alexander Fleming in 1928 with the demonstration of the bactericidal effects of penicillin.

In 1968 Stanley Dudrick, MD, and others[1] began to advocate 4 total parenteral nutrition for patients with poorly functional gastrointestinal tracts and catabolic disease processes. He demonstrated accelerated healing in processes that had previously carried poor prognosis. Since that time we have come to appreciate the extreme usefulness of appropriate supplementation of vitamins, carbohydrates, protein, and lipids by the intravenous or gastrointestinal route in surgical patients. We can aid in healing of wounds, closing of fistulas, clearing of infections, recovery of failing organs, and response to therapeutic agents. Nutrition is one of our more powerful therapeutic resources.

The implications of metabolic manipulation are far-reaching. Investigators are now exploring the metabolic changes accompanying shock and trauma and their reversal with nutritional therapy. We owe gratitude to Dr Dudrick and others who have made the "fourth coming" possible.

---

*Stevens JC: Surgical Nutrition: The Fourth Coming, reprinted from Letters to the Editor. *JAMA* 239:192, 1978.

[1] Dudrick SJ, Wilmore DW, Vars HM, et al: Long-term parenteral nutrition with growth, development and positive nitrogen balance. *Surgery* 64:134-142, 1968.

We have reprinted the above letter to the editor of JAMA because we believe it should be seen by every physician concerned with the nutritional status of hospitalized patients. The letter writer ranks hyperalimentation with some of the monumental medical discoveries of the past—anesthesia, antisepsis and antibiotics. Few who have witnessed the lifesaving benefits of this technique would argue the point.

We at USV are proud of our continuing role in hyperalimentation through the development and refinement of the comprehensive multivitamin infusion M.V.I.®, as well as sponsorship of research and educational programs in parenteral nutrition.

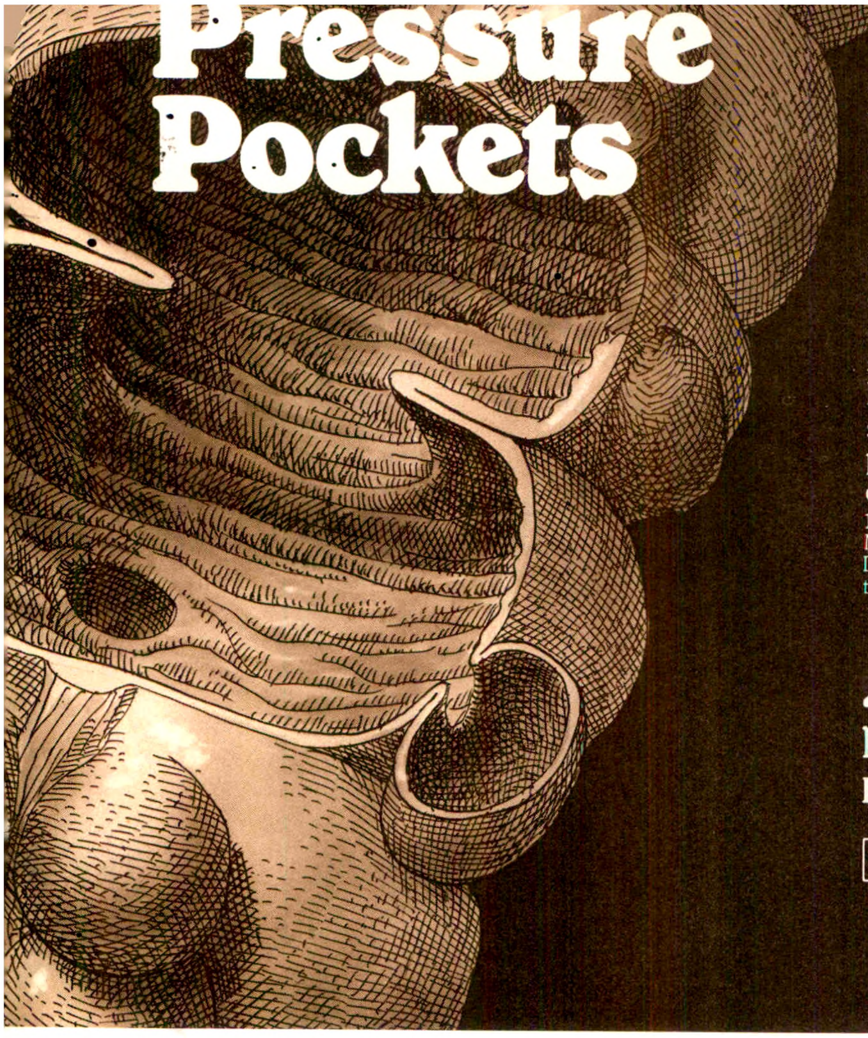
To learn how hyperalimentation may reduc morbidity and mortality in a wide variety o clinical situations, just write us on your letterhead requesting a comprehensive monograph, tape-cassette program and/ film on the subject.

USV LABORATORIES

USV Laboratories, Division
USV Pharmaceutical Corp.
Tuckahoe, New York 10707

HYPERALIMENTATION

M.V.I.® (MULTI-VIT
INFUSION



Pressure Pockets

"Once the diagnosis of symptomatic diverticulosis has been established, treatment is aimed at providing enough bulk in the diet to keep the bowels moving normally."[1]

Metamucil is an effective source of bulk in the treatment of diverticular disease. A bulk laxative containing concentrated dietary fiber, Metamucil restores natural rhythm of elimination by helping to form soft, moist, easy-to-pass stools, and also reduces the intracolonic pressure and possible resulting pain of diverticular disease."[1,2]

1. Behringer, G. E.: Diverticular Disease of the Colon, Hospital Medicine 11:6 (Sept.) 1975. **2.** Davis, R., and Thompson, J. C.: Diverticular Disease of the Colon, Continuing Education for the Family Physician 4:88 (Feb.) 1976.

Metamucil®
psyllium hydrophilic mucilloid
High in dietary fiber/Few calories

SEARLE **Searle Laboratories**
Division of G.D. Searle & Co.
Box 5110, Chicago, Illinois 60680

863

Complications
in Vascular Surgery

***Edited by* HUGH G. BEEBE, M.D.,**
With 18 Contributors.

Outstanding vascular surgeons from all sections of the country have pooled their composite experience and knowledge for this in-depth work. Each has written on a specific vascular complication and gives you the benefit of his expertise in this area. Three objectives are always in view: 1) To help you prevent complications where the causes are known and can be anticipated. 2) To provide you with a clear guide to the management of complications. 3) To establish a foundation of information from which you can deal logically and effectively with problems not described. This work reaps the benefit of significant appraisals of long-term follow-up studies that became possible during the last ten years.

402 Pages • 175 Illustrations • 1973 • $32.00

J. B. LIPPINCOTT CO.
East Washington Square, Phila., Pa. 19105

Please send me:

Complications in Vascular Surgery $32.00

☐ Payment Enclosed ☐ Charge and Bill me

Name ______________________

Address ______________________

______________________ Zip ________

AS 9/79

Lippincott

Histopathology in the Evaluation of Total Pancreatectomy for Ductal Carcinoma

A. FRANCINE TRYKA, M.D., JOHN R. BROOKS, M.D.

From the Pathology and Surgery Departments of the
Harvard Medical School at
the Peter Bent Brigham Hospital,
Boston, Massachusetts

Whipple resections for pancreatic head carcinoma are often inadequate because tumor is left behind in the body and tail. Thirty-six patients have undergone total pancreatectomy for various conditions, of which 25 have undergone total pancreatectomy for *ductal* carcinoma. Thirty-seven per cent of these 25 patients have shown histologic evidence that a Whipple resection would not have adequately removed tumor-bearing pancreatic tissue. Three patients had carcinoma spreading up and along the common bile duct from a primary ductal carcinoma in the head of the pancreas. Four patients had tumor infiltrating in continuity into the pancreatic body and tail at a distance from the palpable tumor in the head well to the left of a Whipple transection site. Five patients had widespread multifocal autonomous tumor involving other areas in the gland but with tumor palpable only in the head of the pancreas. Three patients (12%) died postoperatively. The two year survival rate is 32%, and the five year survival, 19%. Histological factors affecting the survival prognosis include 1) positive nodes, 2) tumor extension up the common duct, and 3) intrapancreatic extension and multicentricity of tumor mandating total pancreatectomy for hope of cure in at least 38% of cases.

IN 1966, following a review of previously performed Whipple procedures for ductal carcinoma of the pancreas, we suggested that 30–40% of patients undergoing such a resection for carcinoma of the pancreas had inadequate resections because tumor was left behind in the body and tail of the gland.[2] Since that time, others have similarly emphasized this histopathologic finding in cancer of the pancreas.[7,8]

Also, it has been known ever since the Whipple procedure was first performed that approximately 40% of deaths from this procedure result from leakage at the anastomosis between the pancreatic tail and jejunum.

The five year survival rate following the Whipple procedure for ductal carcinoma of the pancreas has varied from 0–6%.

These three facts (multicentric histopathologic characteristics of ductal carcinoma of the pancreas, leakage at the pancreaticojejunal anastomosis and low survival rates following the Whipple procedure) prompted us and others at that time to reinvestigate the concept of total pancreatectomy for ductal carcinoma of the pancreas.[7,10,12] At that time it was and to this date is our feeling that the Whipple procedure is still the appropriate operative procedure for patients with ampullary or duodenal carcinoma. Five year survival that follows a Whipple procedure for these tumors is acceptable (25–35%), and not all patients require endocrine or exocrine replacement following a Whipple procedure.[4,14]

The purpose of this present report is to update our histopathologic findings in 36 patients who have undergone total pancreatectomy, with particular emphasis on the 25 patients who have had total pancreatectomy for ductal carcinoma of the head of the pancreas.

Materials and Methods

In the past ten years, 36 patients have undergone total pancreatectomy. Twenty-five of these patients have undergone total pancreatectomy for ductal carcinoma of the head and the pancreas. Table 1 shows the distribution of these cases according to pathological findings. There were no patients with resectable lesions in this series who had carcinoma located primarily in the body or tail of the pancreas, and no patients with carcinoma of ampulla of Vater, duodenum or common duct underwent total pancreatectomy. Our resectability rate for patients with carcinoma of the pancreas has been less than 10%. The reason for this low case accrual appears to be at least in part due to our presently somewhat restrictive indications for total pancreatectomy: patients with regional lymph node metastases are not considered candidates for total pancreatectomy. Total pancreatectomy is performed only if the surgeon, on investigation, is unable to find positive lymph nodes in the celiac, lesser curvature, gastro-

---

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

Reprint requests: John R. Brooks, M.D., Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, Massachusetts 02115.

0003-4932/79/0900/0373 $00.95 © J. B. Lippincott Company

TABLE 1. *Total Pancreatectomy: Disease Distribution*

Diagnosis	Number	Mortality
Ductal carcinoma	25	12%
Cystadenocarcinoma	2	
Insulinoma	4	
Pancreatitis	4	
Total	35	11%

hepatic, retroduodenal or superior mesenteric watersheds and there is no obvious spread to contiguous organs (other than the duodenum). Hermreck et al.'s[5] Stages I and II qualified for resection throughout.*

Although the surgeon may not find positive lymph nodes in these areas, not infrequently the pathologist may find positive "proximate" lymph nodes in, on or near the pancreatic capsule at the time of examination of the specimen under the microscope.

Histopathological Examination

Twenty-one cases were available for review of the pathology. Histological sections varied from 19 to 58 (average 27) slides per case. All of the specimens were fixed in 10% buffered formalin and processed in the routine manner for paraffin embedding. Sections were cut at 4 μ and stained with hematoxylin and eosin. Cases were reviewed to assess the extent of spread of the main tumor mass, the presence of vascular or perineural invasion and the presence of lymph node metastasis. Sections of the body and tail of the pancreas were examined for metastasis and for autonomous carcinoma *in situ* or invasive carcinoma.

Clinical Results

Twenty-five patients underwent total pancreatectomy for *ductal* carcinoma of the pancreatic head. Three patients (12%) in our series died within the 30-day postoperative period. Ten patients died within 12 months of operation of tumor recurrence. Six of these had positive proximate lymph nodes found by the pathologist.

TABLE 3. *Total Pancreatectomy: Mortality and Survival Rates*

Status of Patients	Number	Per Cent
Died postoperatively	3	12.0
Died within 12 months	10	45.0
Died at 24 months	2	9.5
Died beyond 60 months	2	9.5
Alive and well at 120 months	1	36.0
Alive and well at 70 months	1	
Alive and well at 26 months	1	
Alive and well at 8 months	2	
Alive and well at 4–6 months	2	
Alive and well at 2 months	1	

Of the remaining 12 patients, there were seven that lived at least 24 months for a 32% two year survival rate (excluding the three postoperative deaths). Of those seven patients living longer than 2 years, four had multicentric carcinoma found outside the confines of the primary pancreatic head lesion. Two of these seven patients had positive proximate lymph nodes.

Four patients (19%) lived over 5 years (Table 2). Two of these died after five years as a consequence of their tumors. Eight patients are presently alive: one is alive at 120 months, one at 70 months, one at 26 months, two at eight months, two at four–six months and one at two months (Table 3). The mean survival for the group of patients in Stages I and II is 40 months.

Details of the operative technique and postoperative care are recorded in previous publications.[1,6] Suffice it to say that the keynote of the diabetic management of these patients is to maintain an elevated blood sugar (150–200 mg/dl) rather than try to maintain a "normal" blood sugar, so as to avoid the characteristic tendency

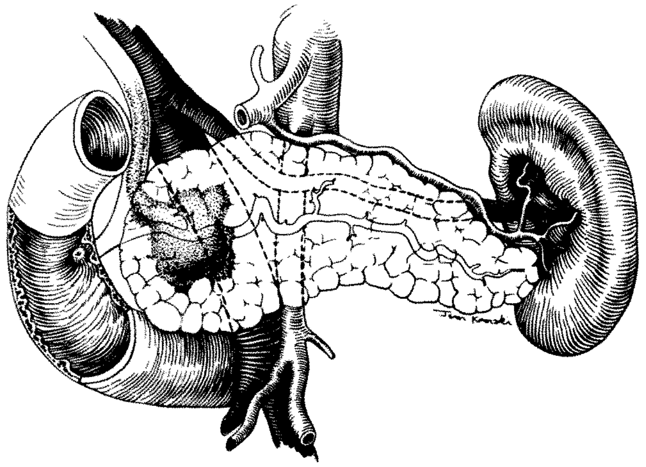


FIG. 1. Tumor spread along the common duct from a carcinoma in the head of the pancreas.

TABLE 2. *Total Pancreatectomy for Ductal Carcinoma: Mortality and Survival Rates*

Number	25
Postop. deaths	12%
Diffuse tumor	37%
Two year survival	33%
Five year survival	19%

---

* Criteria for staging carcinoma of the pancreas: Stage I: Local disease only; Stage II: Invasion to surrounding tissue (duodenum); Stage III: Metastases to regional lymph nodes; Stage IV: Generalized carcinoma.

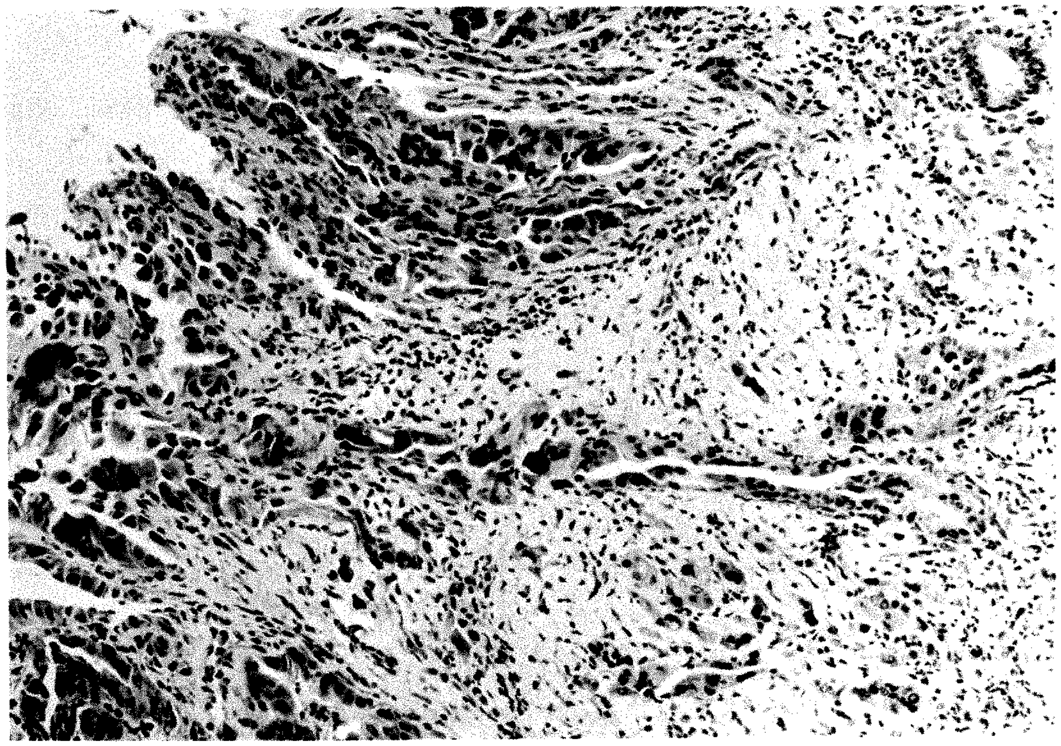


FIG. 2. Carcinoma in the wall of the common duct as it passes through the pancreas. The duct lumen is to the left, its epithelium completely destroyed by tumor.

for these patients to be overresponsive to exogenous insulin.

Histopathology Findings

Thirty-eight per cent of these 25 patients have shown tumor spread beyond the local palpable tumor mass in the head of the pancreas. There appear to be three types of tumor spread.

Type I (3 Patients)

Tumor cells frequently spread up and along the common bile duct from a primary ductal carcinoma in the head of the pancreas. Figure 1 shows an example of this diagrammatically. Figure 2 shows microscopic adenocarcinoma infiltrating the common bile duct wall.

Type II (4 Patients)

This type involves tumor spread in continuity from the primary tumor mass into the body of the pancreas to and beyond the usual site of transection for a Whipple procedure. Malignant tumor in these cases is found well to the left of the superior mesenteric vessels and the retropancreatic vascular tunnel. Figure 3 shows this latter finding diagrammatically. Figure 4 shows the histology in such a patient upon whom a Whipple procedure was performed as a first procedure. Completion of a total pancreatectomy was performed at a second operation 4 weeks later. Jejunal mucosa and ductal carcinoma in pancreatic tissue can be seen in close proximity to each other.

Type III (5 Patients)

In this type, truly multifocal disease occurs with many islands of carcinoma-in-situ and invasive carcinoma separated by regions of normal pancreas. Figures 5 and 6 depict this type diagrammatically, and Figure 7 presents the histologic findings in such a case.

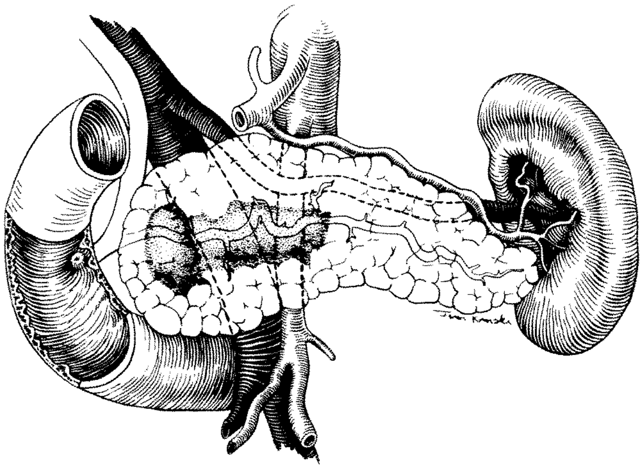


FIG. 3. Tumor spread into the body of the pancreas from a primary lesion in the head.

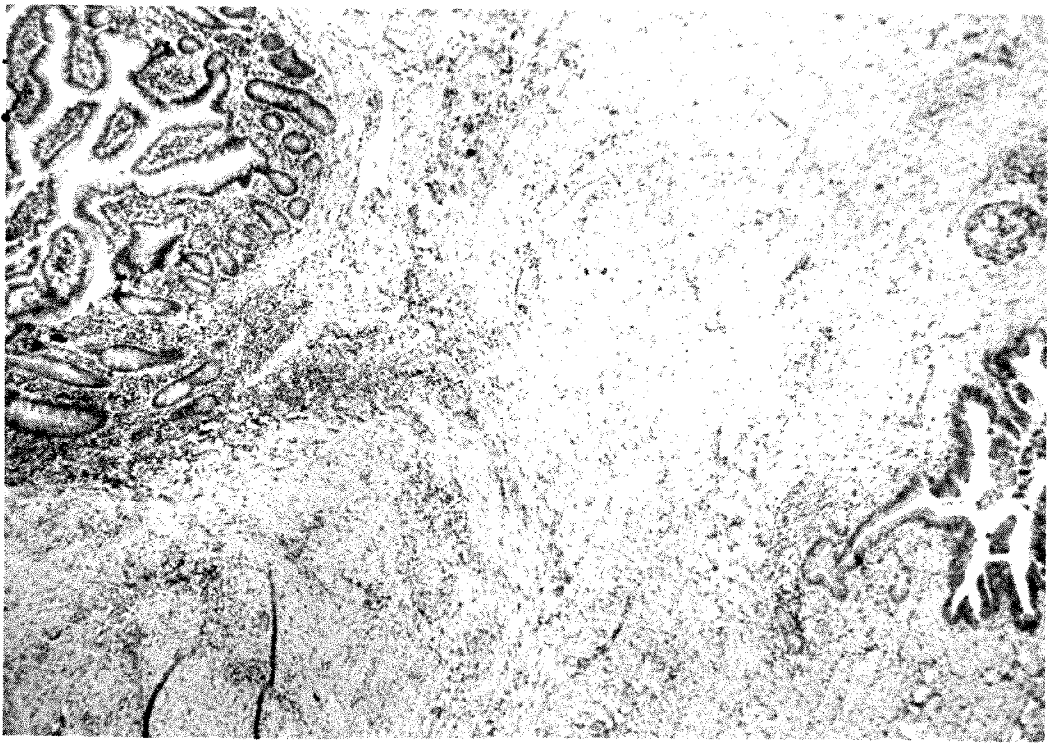


FIG. 4. A section of the previously performed anastomosis between the pancreatic tail and jejunum at the time of total pancreatectomy. The jejunum is seen on the left and residual carcinoma on the right.

Areas of carcinoma can be seen in the body and tail, while the primary carcinoma is in the pancreatic head.

Carcinoma cells may also appear only in the lumen of the ductal system of the tail with normal tissue elsewhere and with the primary tumor being in the head of the pancreas. Figure 8 shows this in diagrammatic form. Figure 9 shows carcinoma cells in the lumen of a duct in the tail and also areas of carcinoma *in situ*. The intraluminal floating cells may be there, having washed back along the duct from the primary tumor, or may be shed from the carcinoma *in situ* lesion in the duct wall.

These Type III multicentric tumor foci appear to represent autonomous islands of new growth.

Discussion

These pathological findings appear to substantiate the concept that ductal carcinoma of the head of the pancreas may be associated with tumor spread distributed throughout the pancreas or autonomous multicentricity in a significant percentage of cases. Sommers et al. in 1954 pointed to associated hyperplasia in ducts

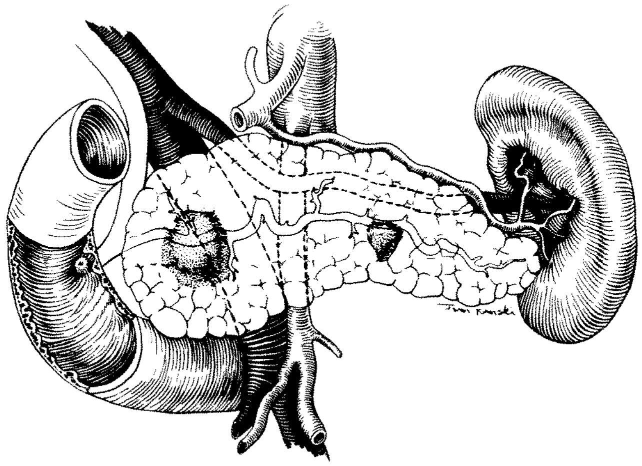


FIG. 5. Multifocal invasive carcinoma separated by normal pancreas from the primary lesion in the head.

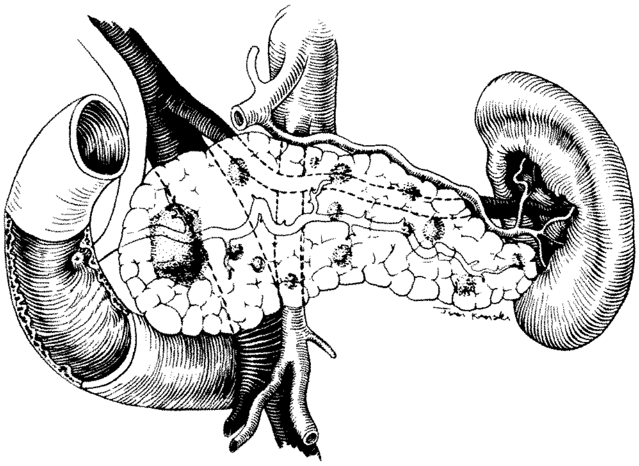


FIG. 6. Multifocal autonomous pancreatic carcinomatosis.

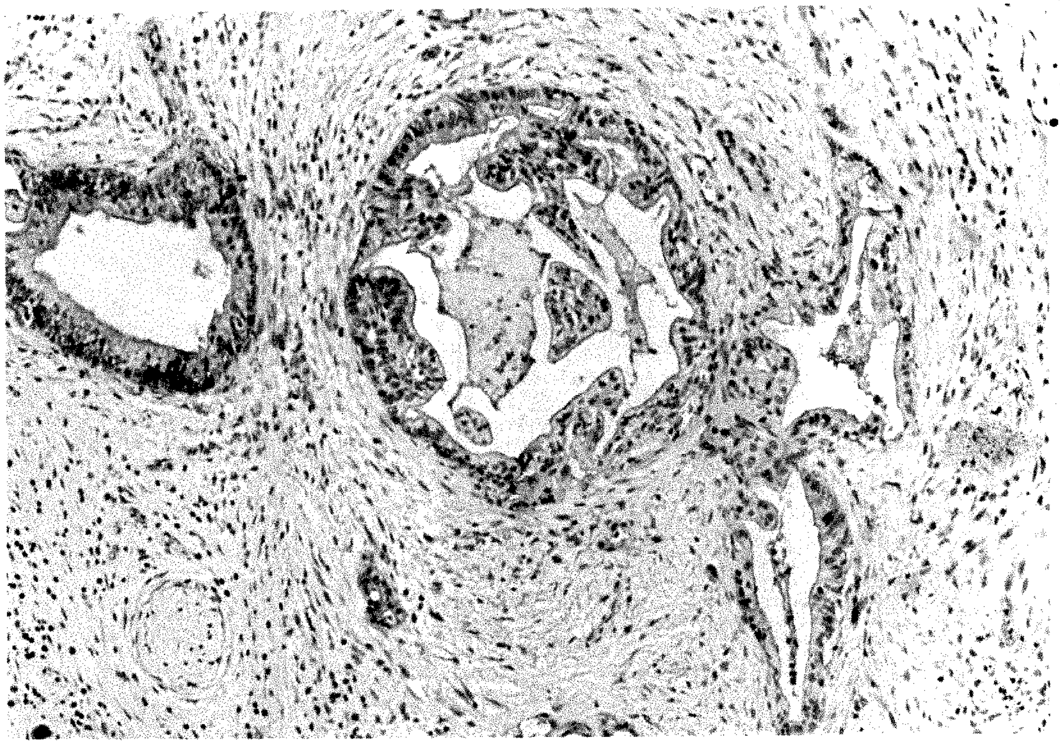


FIG. 7. One of several areas of multicentric invasive carcinoma. This one is in the body of the pancreas separated from the carcinoma in the head by normal pancreas.

in 41% of 141 cases of pancreatic carcinoma.[13] In four of these, papillary hyperplasia, carcinoma *in situ* and invasive cancer were found together in the same specimen, suggesting transition from one to the other.

Only 9% of 150 autopsies on patients without clinical evidence of pancreatic disease showed ductal hyperplasia. However, 28% of 100 autopsies on diabetic patients showed hyperplasia. The higher incidence of cancer of the pancreas in diabetic patients is well known.

Cubilla and Fitzgerald have also reported the finding of autonomous multicentricity in pancreatic carcinoma.[3]

Ross in 1954 described discontinuous tumor 13 cm from the "primary" lesion in the head of the pancreas in one of his four patients who underwent total pancreatectomy and also pointed out that cutting across the pancreatic duct might allow contamination of the peripancreatic area by viable tumor cells in pancreatic juice.[12]

Porter found "microscopic strands" of tumor at the line of resection in "many" specimens from Whipple operations performed before 1949 at the Presbyterian Hospital in New York City.[11] He reported the results with 13 total pancreatectomies done between 1948 and 1957 for carcinoma of the pancreas. His first total pancreatectomy for ductal carcinoma of the pancreas showed foci of adenocarcinoma scattered throughout the tail of the gland.

Mongé et al. reported tumor at the line of resection in five of 28 cases reported from the Mayo Clinic in 1964.[9]

Levin et al.[8] and Pliam and Remine[10] reported 24% multifocal tumor spread in his series of 59 patients with ductal carcinoma of the pancreas who underwent total pancreatectomy. Ihse et al. reported 17% tumor multicentricity in this disease.[7]

These findings and the overall survival results have encouraged us to continue on with total pancreatectomy for localized malignant disease in Stages I and II.

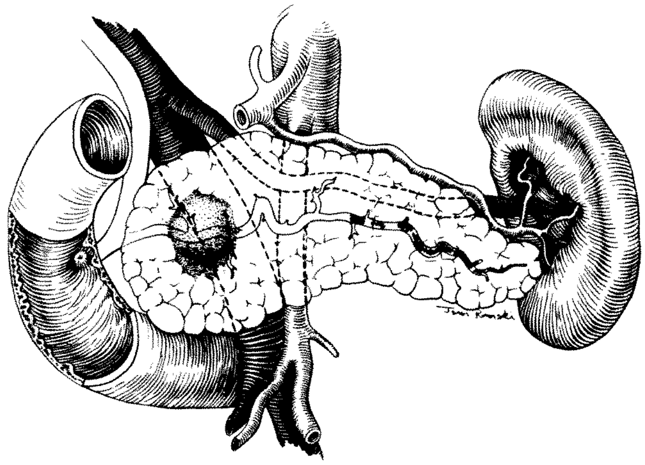


FIG. 8. Carcinoma in pancreatic tail ducts.

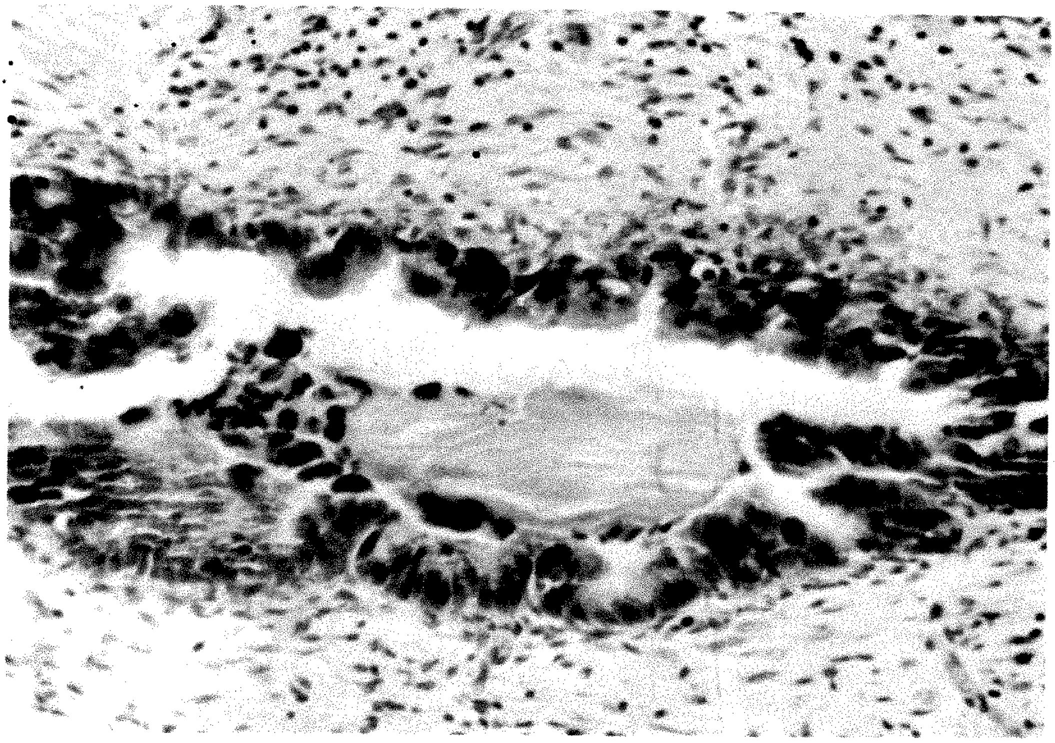


FIG. 9. Carcinoma-in situ and malignant cells in a pancreatic duct lumen at a distance from the primary carcinoma in the head.

Table 4 shows the present survival statistics comparing, retrospectively, total pancreatectomy, the Whipple procedure and a bypass procedure. Figure 10 compares these three operative approaches to cancer of the pancreas in a bar/graph form. The bypass procedure was done in most instances only for palliation. Figure 11 shows life-table curves of survival for these three operative procedures. It seems apparent that total pancreatectomy carries a better prognosis than the Whipple or bypass procedures when employed for Stages I and II pancreatic ductal carcinoma.

Summary

Histological characteristics, as they do with most organ tumors, also affect the long-term survival of patients with carcinoma of the pancreatic head. These characteristics include 1) tumor extension up the com-

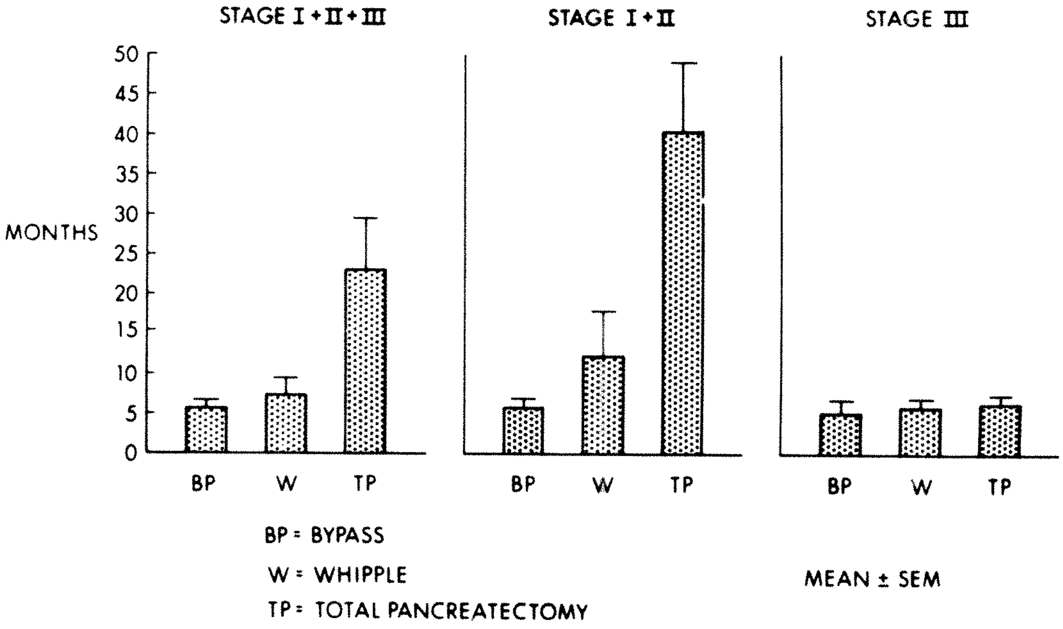


FIG. 10. Ductal carcinoma of the pancreas: survival according to surgical management.

TABLE 4. *Comparative Survival in Patients Undergoing Bypass, Whipple Procedure or Total Pancreatectomy for Cancer of Pancreas*

Procedure	Number of Patients	Per Cent Mortality	Mean Survival		
			Stages I, II, III	Stages I, II	Stage III
Bypass	35	14.28	5.6 mo.	5.8 mo.	5.4 mo.
Whipple	11	21.0	7.6 mo.	12.7 mo.	6.0 mo.
Total pancreatectomy	25	12.0	24.0 mo.*	40.0 mo.†	6.0 mo.

* $p < 0.03$, Total pancreatectomy vs. bypass.

† $p < 0.03$, Total pancreatectomy vs. bypass and Whipple procedure.

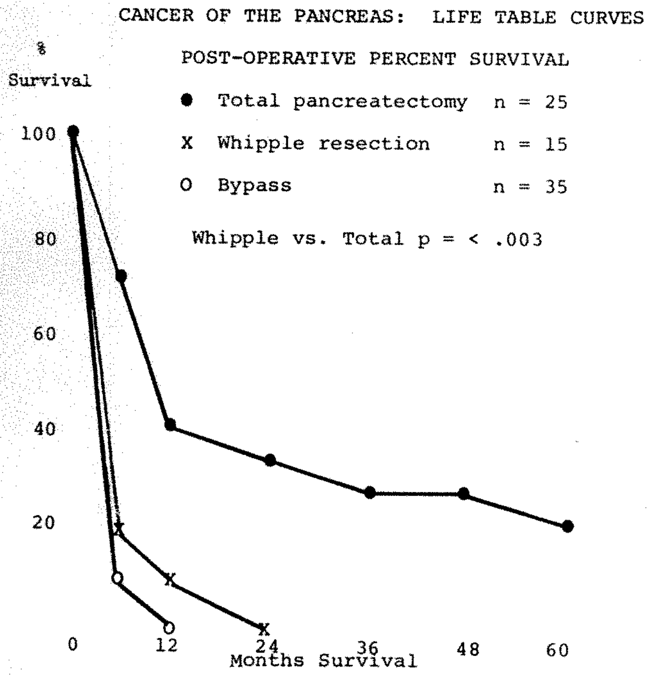


FIG. 11. Cancer of the pancreas:life table curves post-operative percent survival.

mon duct, 2) lymph node positivity for tumor, and 3) intrapancreatic extension and multicentricity of tumor mandating total pancreatectomy for hope of cure in 38% of cases.

Two year (32%) and five year (19%) survival rates are improving and suggest that total pancreatectomy has a significant role to play in surgery for ductal carcinoma of the pancreas.

References

1. Brooks, J. R. and Culebras, J. M.: Cancer of the Pancreas: Palliative operation, Whipple procedure, or total pancreatectomy? Am. J. Surg., 131:516, 1976.
2. Collins, J. J., Craighead, J. E. and Brooks, J. R.: Rationale for Total Pancreatectomy for Carcinoma of the Pancreatic Head. N. Engl. J. Med., 274:599, 1966.
3. Cubilla, A. L. and Fitzgerald, P. J.: Morphological Lesions Associated with Human Primary Invasive Non-endocrine Pancreas Cancer. Cancer Res., 36:2690, 1976.
4. Crane, J. M., Gobbel, W. G. and Scott, H. W.: Surgical Experience with Malignant Tumors of the Ampulla of Vater and Duodenum. Surg. Gynecol. Obstet., 137:937, 1973.
5. Hermreck, A. S., Thomas, C. Y. and Friesen, S. R.: Importance of Pathologic Staging in the Surgical Management of Adenocarcinoma of the Exocrine Pancreas. Am. J. Surg., 127:653, 1974.
6. Hicks, R. E. and Brooks, J. R.: Total Pancreatectomy for Ductal Carcinoma. Surg. Gynecol. Obstet., 133:16, 1971.
7. Ihse, I., Lilja, P., Arnesjo, B. et al.: Total Pancreatectomy for Cancer: An Appraisal of 65 Cases. Ann. Surg., 186:675, 1977.
8. Levin, B., ReMine, W. H., Hermann, R. E. et al.: Panel: Cancer of the Pancreas. Am. J. Surg., 135:185, 1978.
9. Mongé, J. J., Cockerty, M. B., Wollaeger, E. E. et al.: Clinicopathologic Observations on Radical Pancreatoduodenal Resection for Peripapillary Carcinoma. Surg. Gynecol. Obstet., 118:275, 1964.
10. Pliam, M. B. and ReMine, W. H.: Further Evaluation of Total Pancreatectomy. Arch. Surg., 110:506, 1975.
11. Porter, M. R.: Carcinoma of Pancreatico-duodenal Area: Operability and Choice of Procedure. Ann. Surg., 148:711, 1958.
12. Ross, D. E.: Cancer of the Pancreas. A Plea for Total Pancreatectomy. Am. J. Surg., 87:20, 1954.
13. Sommers, S. C., Murphy, S. A. and Warren, S.: Pancreatic Duct Hyperplasia and Cancer. Gastroenterology, 27:620, 1954.
14. Warren, K. and Hardy, K.: Cystadenocarcinoma of the Pancreas. Surg. Gynecol. Obstet., 127:734, 1968.

DISCUSSION

DR. WILLIAM P. LONGMIRE, JR. (Los Angeles, California): I would like to congratulate Dr. Brooks and his associates for their continued, careful analysis of their attempt to improve the results in the treatment of this most difficult malignant tumor.

We also appreciate the advantage of their efforts to eliminate the treacherous pancreaticoenteric anastomosis and any possible residual cancer by a total pancreatectomy. Their results and the findings of others in this country and abroad have enabled us to utilize total pancreatectomy more frequently, although we are still reluctant to employ this procedure routinely for all lesions in the head of the pancreas. Our experience with total pancreatectomy has led us to believe that patients with this condition are not exceptionally difficult to manage with respect to diabetes; most of them require only one injection of 30 or 40 units of insulin each day.

We must remember, however, as Dr. Brooks has stated, some of these lesions that appear to be carcinomas of the head of the pancreas at the time of operation turn out to be carcinoma of the bile duct, or in rare instances, carcinoma of the ampulla or the duodenum.

Inasmuch as fibrosis of the pancreas and dilation of the duct of Wirsung make a pancreaticoenteric anastomosis considerably more reliable in some of these patients, we have therefore restricted consideration of total pancreatectomy to tumors that we initially feel reasonably sure are carcinomas of the pancreas and have either or both of the following findings: (1) the presence of a normal, nonfibrotic parenchyma of the pancreas with a normal, small, thin-walled pancreatic duct, a situation that obviously renders the pancreaticoenteric anastomosis treacherous; (2) a full-thickness biopsy of the pancreas reveals extension of tumor cells into the distal third of the pancreatic parenchyma. Conversely, a fibrotic gland with a dilated pancreatic duct and a negative biopsy of the line of resection would be treated with a Whipple type of operation.

In trying to analyze the information presented in Dr. Brooks' abstract, I believe that use of this technique would have caused us to overlook two of the tumors that he detected by performing a total pancreatectomy.

In our recent review of 232 operations for cancer of the pancreas, most of which were bypass or palliative procedures, a total pancreatectomy was performed on fewer than 3% of the patients, a one month mortality of 17% and an average survival period of 26 months. We compared these figures with a 12% one month operative mortality for 50 Whipple operations and an average survival period of 20 months in patients having a normal biopsy of the residual pancreas.

For other types of localized periampullary lesions and certain of the benign resections of the pancreas, we would like to call your attention again to a method of preserving the pylorus (slide), a procedure that Dr. Traverso and I published about two years ago. We have recently reevaluated 12 of these patients who underwent this operation. All of them demonstrated normal gastric acidity, normal gastric function, and significant reduction of the undesirable digestive side effects of a Whipple resection. In this procedure the duodenum is divided about 2 or 3 cm distal to the pylorus, with careful preservation of the gastroepiploic vein and the circulation along the lesser curvature of the stomach. The pancreas and duodenum are then resected (slide), and in the reconstruction, if total pancreatectomy is not utilized, the jejunum is anastomosed to the residual pancreas, then to the bile duct, and finally, the duodenum is anastomosed directly into the jejunum.

(slide) Postoperative roentgenograms following the ingestion of a barium meal demonstrated normal pyloric function. We think that in selected instances this avoidance of gastric resection and vagotomy has contributed significantly to minimizing the side effects of these extensive resections.

Dr. Isidore Cohn, jr. (New Orleans, Louisiana): I think we all recognize the poor results that are obtained by almost everyone dealing with cancer of the pancreas. What I think many do not realize is that this is a disease that is increasing in frequency in this country, for reasons that are not well understood. It is now the fourth cause of death in this country from cancer of all sites, and that is very different from what many of us learned in medical school.

It is probably for this reason as much as for any other that the National Pancreatic Cancer Project was funded by the National Cancer Institute a few years ago—for the specific purposes of stimulating research into the field of pancreatic cancer, and for doing something to improve the morbidity and mortality of this disease.

Recently, pathologists have, in general, agreed that most cancer of the pancreas is ductal in origin, but it is only recently that there have been some animal tumor models with which the situation could be studied adequately. One of the things the project hopes to do in the near future is to stimulate some controlled clinical studies into the various methods of treatment of cancer of the pancreas, and it is both encouraging and at the same time disappointing to hear a report such as that presented this morning.

Dr. Brooks has been working in this field and talking and writing about it for ten years, and is now only able to report 25 patients that have been operated upon in his series. If we cannot collect a larger series than this to study various methods of therapy, we are never going to define the best way to treat cancer of the pancreas.

When we do propose some protocols for the study of cancer of the pancreas, we hope more and more of you will become involved, so that we can get answers to the problem in a shorter period of time. Certainly the short survival rate for cancer of the pancreas leads it to be an ideal tumor in which to study new methods of treatment. If something is worthwhile, it will show its head promptly. I would hope that when appropriate studies are proposed, many of you in this audience will participate, so that we can come up with an answer.

Dr. William H. ReMine (Rochester, Minnesota): As many of you may know, I have been interested in this subject for a long while, and, I'd like to give you a brief background on our findings.

A few years ago, we reported a group of 239 Whipple resections in which we found that the five year survival rate for lesions of the head of the pancreas was only 18%. After looking those over carefully, we found that one of those lesions was a malignant islet cell tumor. That reduced the results down to about a 12% five year survival rate, and we were not at all satisfied with those figures.

We then reviewed our experience up to that point in time with total pancreatectomy. We were interested in finding out if this was a feasible operation, what kind of life style would the patient have if he or she did survive the procedure whether or not his or her condition would be difficult to control.

We became satisfied that the patient could live a long and successful life. One patient that had had an islet cell tumor that required a total pancreatectomy lived for 29½ years and had a pleasant life along with it. On that basis, we continued our studies and reported our findings up to 1970.

Since that time, our series, which was originally 36 procedures has increased to 122 total pancreatectomies for all types of lesions. Of these, 68 are for ductal lesions or lesions of the head of the pancreas.

Since 1975—and I want to put this in proper perspective in line with current methods of treatment and patient support—we have done 34 Whipple resections with three deaths, for an 8.8% operative mortality. We have done 21 total resections with one death, a 4.7% operative mortality, or, basically, one-half of the operative mortality for the Whipple procedure.

In our original report, 19% of the patients had had multicentric lesions along the pancreatic duct. In our findings since then, now that we have the pathologists interested in looking over the ductal area and the remaining portion of the pancreas, that figure is up to 24%.

The five year survival rate at the present time is three of 12 that are available for long-term study, or a 25% five year survival rate.

In addition to this, we believe that we have what I call a "viable alternative." If we are doing a Whipple procedure for a duodenal lesion or an ampullary lesion or a biliary ductal lesion, we set it up as a Whipple operation and start the anastomosis. If it does not look as though the sutures are going to hold, we feel free to go ahead and take the remainder of the pancreas out and offer that patient a better opportunity for long-term survival and also for a much better morbility prognosis.

The subject was brought up of lesions that extend up the biliary duct to the common duct. We have for a long time followed the suggestion that was made by Dr. John Waugh, whom many of you may remember. It was his finding that many of our recurrences were occurring up along the duct, even with head lesions, especially in the node at the junction of the cystic duct and the common duct. We now extend our resection up above that point, remove the gallbladder, and cystic duct and the associated nodes along the area. I feel this may give us a better opportunity for cure.

Well what then do we have? It is easy to see from the figures that have been presented earlier by Dr. Waugh and the ones that I just presented that we can expect to deny patients a 20–40% opportunity for a cure if we do not do total pancreatectomies. If we do total pancreatectomies we can offer 20–40% more patients a possible opportunity for long-term survival.

Dr. Martin S. Litwin (New Orleans, Louisiana): In Dr. Brooks' usual meticulous and compulsive fashion, he has successfully verified what he postulated in 1968, along with Dr. John Collins;

that is, since ductular carcinoma of the pancreas is a multicentric disease, then a subtotal pancreatectomy or a Whipple operation frequently might not be curative because of unsuspected islands of tumor that might be left behind in the pancreatic remnant.

Another benefit of total pancreatectomy, he proposed, might be that one does not get a pancreaticojejunal fistula in the postoperative period.

Because of the broad nature of Dr. Brooks' paper, I would like to confine my questions and discussion to the "advantages" of total pancreatectomy as opposed to a partial pancreatectomy.

Taking the last advantage first, in our series of Whipple operations we have not seen pancreaticojejunal fistulas since we have been instituting 7–10 days of preoperative intravenous hyperalimentation prior to surgery, and then continuing this regimen for about seven days following the surgical procedure. This allows these chronically depleted patients in strong negative nitrogen balance for a prolonged period of time the opportunity to restore their ability to heal suture lines.

Since 1970 we have performed 11 total pancreatectomies for ductilar carcinoma of the pancreas. Of these 11 patients, seven died within six months of the surgical procedure due to an extraordinary sensitivity to very small doses of insulin. These seven patients all returned to the hospital decerebrate, undoubtedly from insulin shock. We have not been able to control this problem and view it as a major one to the point where we feel somewhat reluctant to perform total pancreatectomy unless there is obvious tumor past the point of resection.

I would like to ask Dr. Brooks whether he has seen problems with insulin dosage. I think it is interesting that these problems with insulin dosage do not appear while the patient is in the hospital during the first three weeks, when there is still a strong hydrocortisone effect. They appear later on, after the patient leaves the hospital. Has Dr. Brooks noted any extreme effects of insulin dosage? If so, how has he handled these? If not, does he have any idea why he has not seen them and we have?

Dr. Clarence Dennis (Stony Brook, New York): Since Dr. Richard Varco and I reported our series 25 years ago certain other things have taken up our time more than doing pancreatectomies. I would like to point out one item and ask three or four questions.

We found that the Watson-Schwartz test for study of the stool for fecal urobilinogen was more reliable than biopsy in determining whether or not neoplasm was responsible for the biliary obstruction. It perplexes me that we do not hear more about this now. It is a cheap way of finding out whether this obstruction is carcinomatous. It certainly is in line with the cost-consciousness that is being imposed upon us by people out side the profession.

Those who perform biopsies of the pancreas, just as Dr. Brooks indicated, have the biopsy as a major determinant of how the lesion is going to be handled. How is the biopsy done? Dr. Varco and I found that performing biopsies on the pancreas when the abdomen was open was not only less reliable than the fecal urobilinogen level, but that it carried a higher risk if resection were not done than as if we went ahead and did the resection.

Does the biopsy disseminate the tumor? We got the impression that it had a tendency to do so, if a radical resection were not done, and perhaps even if it were.

Dr. Lester Dragstedt years back demonstrated in the dog that, subtotal pancreatectomy, leaving 2, 3, 4, or 5% of the gland behind, was responsible for the development of a diabetes which was very difficult to control, much more difficult than as if the entire pancreas were taken out. There are several reports in the literature of simply leaving the uncinate process behind when a radical resection is done. I wonder if those who have trouble with difficultly manageable diabetes after these resections have removed the ucinate process as well.

Dr. Varco and I are pleased to see that now everybody is beginning to agree that one should remove the entire common duct. We came to the conclusion that the greatest longitudinal spread of cancers of the head of the pancreas is along the common duct.

Dr. John R. Brooks (Closing discussion): Dr. Longmire has not come out quite as strongly as I wish he had for total pancreatectomy, but I think his idea for handling the pylorus is a good one.

I tried to initiate a register of total pancreatectomy, as many of you who received letters from me about a year and a half or two years ago know, but I have not had many responses. I was hopeful that we could get a response from those who are doing total pancreatectomy in order to build up more quickly a larger series of these patients and come to a conclusion sooner as to the efficacy of total pancreatectomy. I am counting on Dr. Cohn to help get the total pancreatectomy registry activated.

Dr. ReMine has been a great source of support for total pancreatectomy. His mortality is better than ours; his numbers of patients are greater than ours, but I think the results in our series are all about the same.

Insulin brittleness is a commonly discussed topic. We have seen some brittleness after total pancreatectomy, but we have not lost any patients because of hypoglycemia. We counsel our house staff to keep these patients hyperglycemic. In fact, if the patients spill sugar, we do not become concerned as long as they are not acetonuric. We characteristically keep the blood sugar level at 150–200 mg/dl.

If a patient later has difficulty with insulin brittleness, I am always suspicious that the tumor has recurred. Some of the patients with brittleness later had recurrences, so think recurrence if you see brittleness later on. Keep the insulin dose at a low level, ±20 units NPH, and keep the patient relatively hyperglycemic.

Dr. Litwin mentioned cystadenocarcinoma. We make a strong point of excluding that particular tumor from five year survival statistics because it has a better prognosis.

Finally, Dr. Dennis mentioned fecal urobilinogen as an aid to diagnosis. I am afraid I do not know anything about its use in that regard.

We have performed total pancreatectomy on four patients with carcinoma without an abnormal intraoperative biopsy specimen. We use the True-cut® biopsy needle. We prefer to perform biopsies through the duodenum, if possible, but we rely on clinical data, and go ahead and do a total pancreatectomy if we are convinced that the patient has a tumor and if we are unable to obtain an abnormal biopsy specimen. We have not yet done an inappropriate total pancreatectomy on a patient who had a benign lesion.

The Price of Weight Loss by Jejunoileal Shunt

MARK M. RAVITCH, M.D., ROBERT E. BROLIN, M.D.

In the performance of end-to-end jejunoileal shunt, operative mortality can be nearly eliminated and late deaths largely prevented by assiduous care and follow-up. We attempted to prevent serious complications by regular outpatient visits. However, 703 outpatient visits costing $49.00 per visit failed to improve results. There were 170 readmissions among 64 patients lasting 4–57 days (average hospital stay—16 days per admission at $3,000.00). Twenty-four of those patients alive and followed 18 months or more (53%) sustained adequate weight loss and were free of major problems. Patient satisfaction nevertheless appears high, and when there has been a good weight loss, even severe problems tend to be glossed over by the patient. The ultimate outcome is still unknown, but it seems clear that many of the patients are in a state of controlled malnutrition, which may lead to progressive penalties. We have documented gross pathologic lesions in the bypass enteritis syndrome and draw attention to neurologic sequelae of the bypass, which probably represents deficiency manifestations. Despite brilliant results in some patients and satisfactory results in perhaps half, the cost in life, suffering, dollars, patient and physician time, the uncertain long-term effects, and the unpredictability of the weight loss, all place in question the appropriateness of jejunoileal shunt as the remedy for morbid obesity.

THE CONCEPT of controlled malabsorption by exclusion of measured segments of the bowel, from the alimentary stream in the effort to correct massive obesity, introduced by Kremen et al.[6] and pioneered and intensively studied by Salmon and Reedyk,[14,15] Payne et al.,[11,12] Scott et al.,[16,17,18] Buchwald and Varco et al.,[2,3,4] and others and since put widely into clinical application around the world, has now had more than a decade of extensive experience. When we embarked on a series of these operations in 1972, after some reluctance, we understood that the initial hazards could be overcome by appropriate care and diligence and that in time the patients adjusted and compensated for the induced abnormality and their condition stabilized. This was an experimental program to be performed according to protocol by a single operator. All patients were informed that the operation was experimental, the ultimate results were unknown, the current mortality within a year of operation was expected to be about 5%, that they would have to be permanently and closely followed, return to the hospital for admission on demand, whether for scheduled examinations or for therapeutic indications and that the extent and rapidity of weight loss were unpredictable, except that patients were unlikely to reach the sylph-like figure that they visualized. This was chiefly because in balancing a massive weight loss and, on the other hand, leaving a safe margin of functioning bowel to minimize the likelihood of disaster we would err on the latter side.

From the Departments of Surgery, Montefiore Hospital and the University of Pittsburgh, Pittsburgh, Pennsylvania

Materials and Methods

From 1972 to 1978, 12 male and 52 female patients, ranging in age from 20 to 59 years, underwent jejunoileal bypass at the Montefiore Hospital of Pittsburgh; all but three of them were followed by us for their entire postoperative course. The patients all weighed at least 100 pounds over ideal body weight and usually weighed over 300 pounds, except for a few women five feet tall (Table 1). There was no discovered evidence of endocrine abnormality in any. All had had numerous trials of non-operative weight reduction. Initially, we rejected a good many patients for what we considered to be unstable or pathological personalities, depressive tendencies or intelligence insufficient for reliable cooperation in the subsequent years. Remarkably enough, when a third of the way through the study, we were able to enlist the energetic cooperation of a psychologist and a psychiatrist, and essentially no more patients were rejected for those reasons (except two or three of whom we were so fearful that we did not send them for those studies). The psychiatric and psychological reports were usually that the patient was indeed disturbed or erratic or not very bright, but his/her life was hopeless unless a massive weight loss was achieved. Since there seemed no other way to achieve the weight loss, operation was advised, and the psychiatric–psychological studies after operation usually showed great satisfaction, improved self-image, etc.

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

0003-4932/79/0900/0382 $01.00 © J. B. Lippincott Company

The operation, always a Scott-type end-to-end jejunoileal anastomosis, underwent some modifications. The incision was transverse, supraumbilical and originally crossed the whole right side and extended almost as far on the left; subsequently it was changed so that it usually went only to the midline, dividing the linea alba but not the left rectus. The end of the bypassed bowel originally was implanted in the sigmoid. This was found to be technically difficult, and we thought it resulted in troublesome reflux of gas into the bypassed bowel; therefore we employed the right transverse colon for a time and ultimately came to make the anastomosis to the ascending colon. Our original anastomoses united 12 inches of jejunum, measured on the antimesenteric border (a shorter length of bowel, therefore, than if it had been measured on the mesenteric border) to 8 inches of ileum. This failed to give optimal weight loss sufficiently often that we came to use 11 inches and 6 inches as our standard lengths. All bowel divisions, closures and anastomoses were made with the staplers, and there were no intraperitoneal infections and no anastomotic leaks or fecal fistulae.

A single patient some months after operation vomited repeatedly and showed some intermittent filling defect at the anastomosis. The patient was found at operation (in the original operator's absence from the city) to have a flap of redundant mucosa prolapsing through the anastomosis; the condition was relieved without complication by the excision of this mucosal flap.

Results

This review was undertaken because we were impressed by the number of patients who several years after operation complained of lack of strength, still required medication for the control of diarrhea and continued to manifest or develop anew a variety of complications: sometimes one or another complication would develop late in a patient who had never before had any significant trouble.

The depth of the prior unhappiness of these massively obese patients can perhaps best be measured by their ecstasy over their weight loss, ability to buy clothes off the shelf, bend down and tie their own shoes, go swimming with their children and create jealousy in their spouse and even more by their unwillingness to consider restoration of intestinal continuity. Even the sickest patients with the severest or most prolonged complications fight the idea of alimentary reconstitution, knowing the inevitability of weight gain after it.

It is of some interest that in discussing the pros and cons of the original operation, the complications, mortality, etc., with patients who met the criteria of acceptability for operation, we have several times been successful in dissuading men from the operation but not once a woman. By the same token, the only two patients to ask for a dismantling of the operation were men. One, a steel factory foreman who had no other postoperative problems, said he and his wife considered that the operation had transformed their lives but he feared the pain of renal colic. He had, in fact, had five documented attacks with stones, requiring a ureterolithotomy for one, and had other episodes of renal colic. The other, a man with a public position who had given innumerable exuberant testimonies of his new image and its effect, had had several bouts of metabolic derangement, probably brought on by drinking large amounts of fluid, and was one of those patients who often develop a sudden abdominal distention of astonishing degree. Our female patients have been reluctant to accept the dismantling procedure, even when it was discussed in terms of saving their lives. I do not think there is one who has not said, "I would do it all over again," although a psychiatrist might well take this as meaning, "I must at all costs deny that the risk, the suffering, the economic cost were not worthwhile." Many of the patients were patient-referred, although a sophisticated motivation analysis might offer a variety of explanations for that as well. The evaluation of "patient satisfaction" is particularly difficult after operations for morbid obesity, since the patients are guiltily aware that the obesity was self-induced, and they have more than the usual patient's vested interest in finding that the risks, expense and suffering were all justified.

TABLE 1. *Associated Preoperative Conditions*

Condition	No. Patients
Family history of obesity	34*
Hypertension	15
Dyspnea on exertion	20
Previous cholecystectomy	10
Hemorrhoids	9
Venous insufficiency—lower extremity	5
Degenerative arthritis	5
Adult onset diabetes	5
Pickwickian symptoms	3
Preeclampsia	3
Congestive heart failure	1

* Another 16 patients had no statement concerning family history of obesity; only four patients in the series had negative family histories or other associated conditions.

Discussion

The problem which we have had in the present analysis is just this matter of the pleasure the patients take in their new lives, their repeated expressions of gratitude and our inability to determine how much risk,

TABLE 2. *Response of Obesity-related Diseases to Weight Loss by Jejunoileal Shunt*

Preop. Condition	No. Patients	Re-solved	Im-proved	Unaf-fected
Adult onset diabetes mellitus	5	5		
Hypertension	15	13	2	
Degenerative arthritis (Disability)	5	1	4	
Venous insufficiency	5	3	1	1
Respiratory insufficiency	23	23		

how much discomfort, how much expense is justified in terms of the results achieved and the still uncertain future for all of these patients. Will years of oxaluria result in the renal damage in some percentages of those who do not form stones? Will there be a certain incidence of late hepatic insufficiency? Will the neurologic lesions progress? What we are producing, after all, is a controlled malnutrition.

The serum levels of the common electrolytes are easily measured, but their changes in the total body composition are much less readily so. Of the trace elements we know little. Protein deficiency is clinically obvious in many patients in the continuing brittleness and sparseness of their hair, change in character of their nails, weakness and decreased muscle mass. Osteoporosis and vertebral fracture in a woman who had never had tetany or low serum calcium was disconcerting. Almost all of the patients recognize some weakness, occasionally rather severe, particularly the women. The appearance of neurological symptoms in five patients, i.e., dizziness, ataxia, loss of consciousness, was particularly disturbing

The patients were all discharged and maintained on oral vitamin supplements, calcium, magnesium and potassium and provided with codeine sulfate, Lomotil® or Loperamide® for diarrhea. One "macho" salesman originally took no medication of any kind, finally coming to take codeine occasionally, but never took electrolyte or vitamin supplements. In many others the degree of religiosity of compliance is unknown. All patients were talked to at length before operation, repeatedly in the hospital, again before and after operation and at the frequent postoperative visits concerning the severe thirst they might feel, the necessity for controlling their desire to drink large quantities of fluids, the inevitability of the resultant fluid and electrolyte loss, etc. Yet patient after patient who returned with overwhelming diarrhea or electrolyte imbalance—hypokalemia, hypocalcemia—admitted to having drunk large amounts of fluid and listened in wide-eyed innocence when given the explanation once again.

Four of our patients died. Two died of liver failure at eight and six months after operation. Both were patients who would not or could not eat, who vomited regardless, who lived in rural Pennsylvania and were difficult to bring to the hospital. Both came early in our experience, when we had not adopted our policy of immediately hospitalizing any patient with hepatic dysfunction and had not yet learned the effectiveness of amino acid infusion in 5% glucose for such patients.[11] A third patient who at times had severe hypokalemia and hypocalcemia died suddenly at home, a few days after having been seen with a modest hypokelemia 10 months after operation. The medical examiner's postmorten study showed no cause for death. The fourth patient lost weight inadequately after her 12 in. to 12 in. shunt, had a reversion and lost massively and would eat and do well in hospital but vomited and starved at home and was brought in for reconstitution. She was placed on conventional hyperalimentation, with 25% glucose, went into coma and died—a risk of which we were not aware.

We had two instances of postoperative ventral hernias, no eviscerations, a single severe subcutaneous infection and 11 lesser infections. One patient required overnight tracheal intubation, a woman of 467 pounds. All of our patients were operated upon with the head of the table depressed 15° to empty the leg veins and decrease the likelihood of pulmonary embolism.[7] Episodes which seemed to represent pulmonary embolism occurred in three patients.

In short, this is an operation which we are persuaded can be performed with a very low immediate risk, even in these large patients, and from which we are confident late mortality can be largely eliminated by appropriate care, with the occasional need for a timely reintervention. The determination of the value of the operation will have to be made on an estimation of the quality of life to be lived, the significance of the complications and the long-term results. We are accustomed to tell our patients that they are well aware that if they remain hugely obese, their life expectancy will be shortened and they will be more likely to develop hypertension and diabetes. Fifteen of 64 had hypertension before operation; it was relieved in 13 and improved in two. Five of 64 had diabetes before operation, and all were able to discontinue medication for the diabetes (Table 2). And, of course, after operation upon patients with progressive disability, dyspnea, alarming tachycardia on slight exertion or pickwickian picture before operation, one can say that whatever their present problems, they might not now be alive but for the beneficial effects of the massive weight loss.

The record of complications in our hands is not dissimilar to that reported by others.[13,17,20]

Early postoperative morbidity is summarized in Table 3. Five patients had prolongation of their hospital stay due to excessive diarrhea, which eventually responded to codeine or Lomotil. Nausea and vomiting prolonged the hospitalization of three patients.

The nausea in patients with jejunoileal shunt deserves special comment. Many of them, in almost the same words, will say, "I get queasy when I wake up in the morning," and, for many, vomiting induced by tooth brushing is the chief vomiting problem. Others vomit alarmingly often, and in some the resultant starvation at a time when they should have a large food intake is dangerous; it was fatal in two patients who died with jaundice. The patient with a vomiting problem will often say, "I can't stand the smell of food." We thought the vomiting was usually not psychogenic. Occasional patients still vomit, at times years after operation, but they usually do not mention it unless specifically asked.

We have mentioned the 12 infections in the subcutaneous fat, one of them major. Nine patients had urinary tract infections (all patients had indwelling urinary catheters for at least 48 hours). There was one patient with pneumonia, and we have mentioned the three presumed pulmonary emboli, none major.

The total number of patients with early complications was thus 21 (32%). Forty-five of the 64 patients (70%) were readmitted to the hospital for late sequelae. In all, there were 170 such admissions ranging from four to 57 days, 16 days on the average, at a 1977 cost of $3,000.00 each admission, despite the fact that we tried to treat patients on an outpatient basis for diarrhea and mild electrolyte imbalance.

We recognized electrolye imbalance as a problem in 31 patients (almost 50%), and 11 required hospitalization, presenting with weakness, muscle cramps, paresthesias and occasionally carpopedal spasm. All 31 had hypokalemia, 19 had hypocalcemia, and 13 had hypomagnesemia. The relative severity of the electrolyte disturbances is seen in Table 4. While excessive diarrhea—frequently in patients who admitted to massive fluid intake and then "forgot to take" codeine or Lomotil—preceded the episode of electrolyte imbalance, we saw several patients with severe hypocalcemia and hypomagnesemia who claimed to have only three or four formed stools daily.

TABLE 3. *Early Postoperative Complications*

Complications	No. Patients
Wound infection	12
Gastrointestinal distress*	9
Urinary tract infection	8
Pulmonary embolus	3
Ventral hernia	2

* Includes nausea, vomiting, bloating and diarrhea which prolonged the patient's hospital course.

TABLE 4. *Electrolyte Imbalance*

	No. Patients
Hypokalemia	
K = 3.1–3.5	16
K ≤ 3.0	15
Hypocalcemia	
Ca = 7.1–8.8	11
Ca ≤ 7.0	8
Hypomagnesemia	
Mg = 1.1–1.8	7
Mg ≤ 1.0	6

We have documented vitamin A deficiency by decreased vitamin A levels in two patients with pathognomonic skin and ocular lesions which disappeared with vitamin supplementations. In at least three patients a fiery red, smooth, painful tongue and rhagades indicated overt vitamin B insufficiency.

Hospitalization was indicated for nausea, vomiting and diarrhea in 27 patients. One patient complained of stools "all day long" and claimed no relief from frequent doses of codeine, but in spite of this there was no evidence of electrolyte disturbances, and we felt forced to restore the normal alimentary pathway. On the other hand, in 13 patients there were nausea, vomiting and abdominal cramps without excessive numbers of daily stools (more than six). These patients frequently had a distended abdomen at such times and showed distended loops of (bypassed) bowel in the x-ray films.

Nine patients were considered to have some degree of hepatocellular dysfunction. In five, the elevation of serum bilirubin was minor and the hepatocellular enzymes elevated to levels less than three times the upper limit of normal. All of these patients had nausea, vomiting and abdominal pain. We have described the two deaths from liver failure, and the patient who died unexpectedly at home had earlier mild evidence of impaired liver function. One patient was hospitalized twice with moderately severe symptoms, mild icterus and aberrations of hepatic function and responded to rest and intravenous fluids. On a third occasion, she was feeble and deeply jaundiced, with hepatic enzymes five times the normal, and unable to take nourishment by mouth. She responded dramatically to 2 weeks of intravenous amino acids and has had no further suggestion of hepatic dysfunction in over two years. An additional patient was operated upon for hepatic failure at a military hospital, and her functional segment of small intestine was lengthened, reversing her hepatic dysfunction at the expense of a 30 lb. weight gain in the first 3 months after operation.

Eight patients have had renal calculi, all calcium oxalate; two of these have had multiple episodes. We have mentioned one patient, who in one episode required ureterolithotomy and whom we reconverted, and we plan reconversion in the other patient with multiple episodes. We agree with O'Leary et al.[9] that urinary oxalate is so frequently elevated in the first months after jejunoileal shunt that the determination has no prognostic value. In at least one of our patients with an oxalate stone, the urinary oxalate determination performed some time earlier was within normal limits.

Significant anemia was found in 23 patients, long after the operative event. (No patient required transfusion during the operative admission, except for the patient with an extensive wound infection.) Of the 14 with hemoglobin of 10–12 gm, the red blood cell indices were normochromic and normocytic in ten. In two patients, the anemia was megaloblastic and responded to folate and vitamin B_{12}. In nine patients hemoglobin was less than 10 gm. Three of these were discovered to have blood in the stool more or less constantly; the other nine had no consistent red blood cell picture nor was the cause for the anemia found by extensive hematological investigation. In all, there were 12 patients with normochromic-normocytic indices suggesting iron deficiency.

The occurrence of troublesome diarrhea was variable and not quite universal. Some patients took antidiarrheal drugs regularly, others only "for safety" or after episodes of diarrhea, some almost never. An occasional patient reported only one or two stools per day. Many patients preferred diarrhea to the bloating cramps and distention which accompany use of codeine or Lomotil. Anal burning, pruritus, hemorrhoidal protrusion and bleeding at stool were common. Five patients required minor anorectal operations, all with relief, usually for fissure. A number of patients were troubled at times by incontinence, especially at night. Most patients had their stools principally in the morning and evening, but some have never stopped having to get up at night. The unbearably foul odor of stools and flatus was a problem to all. Patients learned that even for the passage of flatus it was well to retreat to a bathroom and then to open the window. In some instances, marital problems resulted.

The entity called bypass enteritis[10] produces for the most part nonspecific symptoms of bloating, pain, abdominal distress and diarrhea. We had 12 patients repeatedly hospitalized for such symptoms, usually responding to a period of bed rest and intravenous alimentation. In three patients we had unequivocal evidence of such disease in the small bowel. One patient early in our experience was operated upon when x-rays disclosed pneumoperitoneum, although the clinical picture was not that of peritonitis. Pneumatosis intestinalis, but no perforation, was found, and she recovered, although she is one of the two who later died from hepatic insufficiency. A number of reports have mentioned pneumatosis cystoides intestinalis and pneumoperitoneum[5,8,19] occurring in patients after jejunoileal bypass. A second patient, who had had troublesome diarrhea and many episodes of hypokalemia, came in with severe abdominal pain and a palpable mass. Exploration demonstrated several feet of the distal bypassed bowel had thickened, enlarged and became firm and an angry, dark reddish purple and was covered by numerous conspicuous, tortuous vessels. Nothing was done, and her symptoms subsided. This woman, who had had bilateral knee joint replacements for crippling osteoarthritis and had been in a wheel chair when we first saw her, a year later was walking well without any aids and was having less trouble with diarrhea and maintenance of electrolytes, which had been a recurrent problem; however, she had several massive hemorrhages from her intestine and underwent reconstitution. The bypassed bowel was thickened but no longer inflamed externally. Histologic examination of the amputated end showed evidences of mucosal and submucosal inflammation. She has not bled since. The third and most dramatic example occurred in a man whose weight had gone from 300 to 180 pounds in 18 months. He developed a severe secondary anemia but remained otherwise well, vigorous and enthusiastic. A vagotomy and pyloroplasty, done in his hometown, were unavailing. Our colonoscopy showed the ileum, which had been anastomosed to the transverse colon, to be the seat of large, discrete, sharply outlined ulcers, the mucosa between them appearing not inflamed. At operation at 2 1/2 years, the involved segment, found to be about 18 in. long, was resected. The patient continued as before without the slightest symptoms, eating ravenously and maintaining his new physique, but he resumed bleeding. After 4 1/2 months, we reoperated, resected another thickened, ulcerated distal segment and converted his Scott-type end-to-end operation to a Payne end-to-side operation. In the 36 months since then, he has gained 35 pounds, still 115 pounds less than his original weight, and has bled no more. It is of some interest that his sister, also with a superb weight loss but with polymyositis, had a severe chronic anemia and ultimately, after 5 years and 3 months, had a lengthening, elsewhere, of her functioning bowel because of hepatic dysfunction, with a substantial gain in weight of 30 pounds in 3 months. Three patients had severe, recurrent, migratory polyarthralgia, which ultimately cleared in two, but which in a third has been intermittently present and is at times disabling after 5 years.

The puzzling neurological manifestations in five patients have consisted of attacks of dizziness, instability,

TABLE 5. *Pattern of Weight Loss*

	Preop	1 mo.	3 mo.	6 mo.	9 mo.	12 mo.	18 mo.	24 mo.	36 mo.
Average weight	317.7	281.1	273.6	247.6	227.4	222.0	198.7	187.7	176.6
No. patients	64	64	64	64	59	56	49	42	28

tilting to one side in walking, walking with a wide base and, in two cases, not personally observed by us, a comatose state of some hours' duration, with spontaneous recovery. Some of these patients with neurological problems have been patients otherwise difficult to handle. One, on the other hand, was a steel hauler who had gone back to work promptly, had a splendid weight loss and no problem with diarrhea or electrolytes. Repeated and extensive study of these patients yielded only the information that one patient was considered to have multiple sclerosis on the basis of spinal fluid studies. If so, she has had a remission for over 2 years now. Two patients required hospitalization for severe psychoses, one with alternating moods of euphoria and depression, delusions and hallucinations, the other with a severe reactive depression manifested by complete withdrawal. Both responded very satisfactorily to psychiatric treatment and have had no further difficulty. Both were among the patients who had difficulty in accepting their new slender selves as "me." Neither had presented any other major problems.

One man, previously a "jolly fat man," coincident with a massive and relatively uncomplicated weight loss, became violent and abusive toward his family and required two admissions for episodes of severe disturbance; he ultimately adjusted. One patient developed seizures, had an abnormal EEG, and on anticonvulsants has had no further episodes.

Table 5 shows the pattern of weight loss achieved, and Figure 1 shows the slope of the weight loss curve expressed as the cumalative percentage of initial weight reached per unit time. There was substantial variation in the rapidity and extent of weight loss. Of 49 patients followed more than 18 months, in 26 the weight had stabilized by 18 months, while 23 continued to lose weight. Five of these were stable by 24 months, the remainder leveled off in the 3rd year.

Despite the known variation in the length of bowel from one individual to another, the imprecision of the actual measurement and the problem imposed by the varying appearance of Treitz's ligament and the occasional covering over of the ileocecal junction by fat, there was a remarkable difference in weight loss, with small changes in the length of residual functioning small bowel. Figure 1 compares the weight loss in 12 patients with 19 in. or more of functioning small bowel (all but one operated upon early in the series) with the 52 patients whose functioning small bowel measured 18 in. or less. The weight loss curves for these two groups begin to separate at about 12 months postoperatively. By 18 months, the cumulative percentage of weight lost by the 19 in. or more group was 28%, as compared to the 37% in the 18 in. or less group. The patients with the longer segments flattened their weight loss curves at 18 months, and at 36 months all the patients with the shorter segments had lost at least one-third of their preoperative weight, whereas only three of 12 of the other group had lost that much.

We were troubled by the fact that some patients lost inadequate amounts weight after what was a standardized operation—two in the 19 in. group and two with 11 inches of jejunum and 7 inches of terminal ileum. At reoperation, as Scott[16] and others have shown, the jejunal segment was longer, thicker and dilated, and the ileal segment was less so.

Viewed quantitatively, the complications resulted in 170 hospital admissions of 4–57 days in these 64 patients, as of the time this analysis was done. The average length of hospitalization was 16 days at an estimated cost of $3,000.00 per 16 day admission (costs based on the rates in December 1977, no allowance for subsequent inflation).

There had been 703 outpatient visits, 11 per patient (at a cost each time of $49 for laboratory determinations) and innumerable phone calls in addition. Two patients had more than ten admissions and 30 follow-up visits each.

Given the assumed shortened life expectancy with

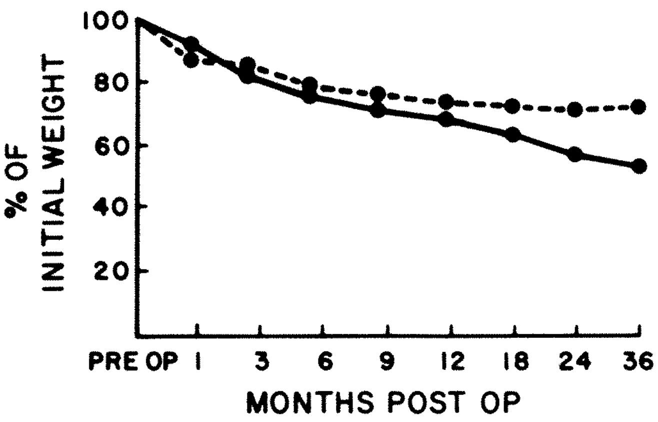


FIG. 1. Weight loss over a three year period. Group A (broken line) includes all patients whose combined jejunal and ileal lengths were ≥ 47.5 cm (19 in). Group B (solid line) includes all patients whose combined jejunal and ileal lengths were ≤ 45 cm (18 in).

massive obesity, the known increased risk of diabetes and hypertension and the poor quality of life for the monstrously obese and in the light of the almost universal failure of non-operative measures, it was hoped that jejunoileal bypass would be an effective and acceptable form of therapy. The operative mortality is or should be very low and the long-term mortality can be minimized, but we have come to the conclusion that even with close follow-up and prescription of multiple medications, the late postoperative sequelae have not been predictable or preventable. As of December 1977, 11% of our patients had undergone restitution; the number continues to grow. Only ten of 45 patients whose weight has stabilized have not required readmission to hospital, and two of those stabilized failed to lose 33% of their preoperative weight. Of the entire 45, only 24 (53%) lost *more* than one-third of their preoperative weight *and* were doing well with their bypass, somewhat less than the 66% good results quoted by Scott et al.[17]

References

1. Ames, F. C., Copeland, E. M., Leeb, D. C. et al.: Liver Dysfunction Following Small-bowel Bypass for Obesity. Non-operative Treatment of Fatty Metamorphosis with Parenteral Hyperalimentation. JAMA, 235:1249, 1976.
2. Buchwald, H., Moore, R. B. and Varco, R. L.: Ten Years Clinical Experience with Partial Ileal Bypass in Management of the Hyperlipidemias. Ann. Surg., 180:384, 1974.
3. Buchwald, H. and Varco, R. L.: A Bypass Operation for Obese Hyperlipidemic Patients. Surgery, 70:62, 1971.
4. Buchwald, H., Varco, R. L., Moore, R. B. and Schwartz, M. Z.: Intestinal Bypass Procedures. Partial Ileal Bypass for Hyperlipidemia and Jejunoileal Bypass for Obesity. Curr. Probl. Surg., 1975.
5. Drenick, E. J., Ament, M. E., Finegold, S. M. et al.: Bypass Enteropathy. Intestinal and Systemic Manifestations Following Small-bowel Bypass. JAMA, 236:269, 1976.
6. Kremen, H. J., Linner, J. H. and Nelson, C. H.: An Experimental Evaluation of Nutritional Importance of Proximal and Distal Small Intestine. Ann. Surg., 140:439, 1954.
7. McLachlin, A. D., McLachlin, J. A., Jory, T. A. and Ramling, E. G.: Venous Stasis in the Lower Extremities. Trans. Am. Surg. Assoc., LXVIII, 1960.
8. Menguy, R.: Pneumatosis Intestinalis After Jejunoileal Bypass. JAMA, 236:1721, 1976.
9. O'Leary, J. P., Thomas, W. C. and Woodward, E. R.: Urinary Tract Stone After Small Bowel Bypass for Morbid Obesity. Am. J. Surg., 127:142, 1974.
10. Passaro, E., Jr., Drenick, E. J. and Wilson, S. E.: Bypass Enteritis. A New Complication of Jejunoileal Bypass for Obesity. Am. J. Surg., 131:169, 1976.
11. Payne, J. H. and DeWind, L.: Surgical Treatment of Obesity. Am. J. Surg., 118:141, 1969.
12. Payne, J. H., DeWind, L., Schwab, G. E. and Kern, W. H.: Surgical Treatment of Morbid Obesity. Sixteen Years of Experience. Arch. Surg., 106:432, 1973.
13. Phillips, R. B.: Small Intestinal Bypass for the Treatment of Morbid Obesity. Surg. Gynecol. Obstet., 146:455, 1978.
14. Salmon, P. A.: The Results of Small Intestine Bypass Operations for the Treatment of Obesity. Surg. Gynecol. Obstet., 132:965, 1971.
15. Salmon, P. A. and Reedyk, L.: Fatty Metamorphosis in Patients with Jejunoileal Bypass. Surg. Gynecol. Obstet., 141:75, 1975.
16. Scott, H. W., Jr., Dean, R. H., Shull, H. J. et al.: Further Considerations in the Use of Jejunoileal Bypass in Patients with Morbid Obesity. Bull. Soc. Int. Chir., 33:378, 1974.
17. Scott, H. W., Jr., Dean, R. H., Shull, H. J. and Gluck, R.: Results of Jejunoileal Bypass in Two Hundred Patients with Morbid Obesity. Surg. Gynecol. Obstet., 145:661, 1977.
18. Scott, H. W., Jr., Sandstead, H. H., Brill, A. B. et al.: Experience with a New Technique of Intestinal Bypass in the Treatment of Morbid Obesity. Ann Surg., 174:560, 1971.
19. Sicard, G. A., Vaugh, R. and Wise, L.: Pneumatosis Cystoides Intestinalis: An Unusual Complication of Jejunoileal Bypass. Surgery, 79:480, 1976.
20. Starkloff, G. B., Donovan, J. F., Ramach, K. R. and Wolfe, B. M.: Metabolic Intestinal Surgery. Its Complications and Management. Arch. Surg., 110:652, 1975.

DISCUSSION

DR. J. HOWARD PAYNE, SR. (Los Angeles, California): A search of the literature showed innumerable publications on the various surgical approaches to the morbidly obese patient since 1965. Our first experience was in 1956, but our first publication was not until 1963. It took us seven years to arrive at the conclusion that the jejunocolic bypass was hazardous and should be abandoned. We now have 23 years of experience with the surgical approach to hyperobesity. We still see and follow our first patient to undergo surgical therapy for malnutrition morbid obesity. Every effort has been made to provide for the patient's long-term care, clinical observation and problems. With this background, we have periodically reported our results to provide a perspective for other investigators, with our approach, and to the adventuresome who are trying other surgical methods to reduce weight.

The bypass with the end-to-end anastomosis, known as the Scott procedure, decompresses the bypassed bowel into the colon. There will be regurgitation of large bowel content into the bypassed bowel whether the ileocolic anastomosis is into the cecum, transverse colon or sigmoid. In may opinion, this is the primary cause of one of the relatively new problems, namely, the so-called bypass enteritis syndrome. These problems are responsible for many revisions and takedown operations. One patient has described the syndrome as "the bloats and the blahs."

The gastric bypass has been changed so many times that I cannot keep up with it. It is inappropriate to draw conclusions with only one year of follow-up study. We are now seeing failures and devastating complications. I have never done a gastric bypass but have consulted with patients and their doctors relative to the procedure and their problems. These data could supply enough information for a separate manuscript. The use of large stapling devices in the upper abdomen in a 400 pound patient is difficult and uncertain. The most skilled surgeons have problems maneuvering in the subdiaphragmatic area of the celomic cavity even in the patient who is not obese.

With the foregoing in mind plus many happy alumni, we have continued to do the jejunoileal bypass using 35 cm of proximal jejunum anastomosed end-to-side to the distal 10 cm of the ileum with a minor modification designed to prevent reflux into the bypassed segment. This procedure has been named by others as the

Payne procedure. We have classified our results: excellent, 65%; satisfactory, 25% and failures, 10%. I do not use the stapling machine.

It is imperative that patients selected for this operation continue to meet the original strict criteria. Some form of surgical procedure appears to be the only method of weight reduction that does not depend on impractical and dietary restrictions. Unfortunately, too many of these operations are being done on poorly selected patients by surgeons who are not fully aware of all the pre- and postoperative problems.

I do not agree with the authors' conclusions. I do think that appropriate investigations should be continued. The results are worthwhile in spite of the costs.

Dr. H. William Scott, Jr. (Nashville, Tennessee): I will comment predominantly on the experience that we have had from 1966 through 1978 with 225 massively obese patients who underwent jejunoileal bypass.

(slide) The slide shows findings in addition to obesity in these 225 patients, and you will note that hyperlipidemia occurred in 112 patients, 62 had gallstones; 39, diabetes; 31, diastolic hypertension, and so on.

The early postoperative mortality was 2%.

(slide) This slide shows the changes in body weight in four study groups based on different dimensions of jejunoileal bypass, and the curves of the mean change from 100%, representing original preoperative weight plotted against time. The greatest sustained weight reduction occurred in patients who had total incontinuity small intestine shortened to 45–50 cm.

The early postoperative complications, such as wound seroma, wound infection and thrombophlebitis, which Dr. Ravitch has detailed, were quite similar in our group, and occurred in 22%. Prophylactic efforts, however, have almost eliminated these surgical complications in the last 100 patients.

Major metabolic complications include oxalate urinary stones in 15% and episodes of the enterohepatic syndrome of hepatocellular injury in 12% of patients. There were four late deaths of liver failure.

We have learned from patient studies, from animal models, and the work of others, that the hyperoxaluria and urinary stones result from the short bowel, and not from the bypassed gut. All patients are currently instructed prior to discharge and repeatedly during follow-up studies to follow a high protein, low fat, low oxalate diet, in an effort to reduce the hyperoxaluria and the incidence of oxalate stones.

In contrast, the flu-like syndrome of nausea, vomiting, hypergeusia, myalgias and prostration, accompanied by elevation of liver enzymes and later by icterus and hepatomegaly, reflects hepatocellular injury from absorption of toxic metabolites of heavy bacterial growth in the bypassed small bowel. All patients are taught to recognize these symptoms, and prompt treatment with oral antibiotics—we prefer Flagyl, (micronidazol)—and high protein diet eliminates the symptoms in a few days in most instances. Resistance to these simple measures requires hospitalization for enteral or parenteral hyperalimentation and more potent antibiotics, and, if necessary, takedown of the bypass.

Metabolic benefits include mean weight loss of 45–50%, reduction in serum cholesterol and triglyceride level of 40–60%, and uniform relief of adult onset diabetes.

(slide) These show the changes in a group of 71 patients who had Frederickson Type IV hyperlipoproteinemia in this group, preoperative cholesterol plotted in the white bar graph, and triglyceride in the same; and after jejunoileal shunt there was a considerable drop, averaging 40%, in baseline cholesterol, and 50–60% in triglyceride.

(slide) The same in true with familial hypercholesterolemia, plotted here, the baseline just under 300 mg/dl, and the triglycerides elevated in the same range, with a drop of 50%, on the average, in cholesterol level following jejunoileal shunt, a little less regular pattern of drop with the triglyceride.

With current dimensional considerations, good results have been achieved in 75% of our patients. However, certainly morbidity and mortality risks are significant, and I must agree with Dr. Ravitch that these limit wide application of the procedure.

Gastric stapling is indeed an attractive alternative for obese patients who are not hyperlipidemic.

Dr. Max Raymond Gaspar (Long Beach, California): I bring to your attention another approach to this problem which was conceived by Dr. Larry Wilkinson, of Albuquerque, with the idea of reducing gastric reservoir capacity. His idea was to plicate the stomach upon itself, and then wrap it with a mesh.

He found in animals that it was necessary to use a mesh to maintain the plication, or the animals would distend the stomach.

At first, this was done by plicating the greater curvature. I have followed Dr. Wilkinson's approach, and we have revised the operation to do a Nissen fundoplication high on the stomach, and then to fold the stomach upon itself below the plication. Dr. Wilkinson wraps the stomach with a Marlex mesh; I have started using a Teflon mesh. We put a Levaculator tube into the stomach to calibrate the size of the stomach at 36 French.

Dr. Wilkinson has operated on 26 patients, the oldest 2½ years ago. He has followed eight patients for more than a year. They have lost an average of 80 lbs. I have operated on seven patients. They have had satisfactory weight loss to date, with no metabolic complications. I have avoided this operation in patients who claim thay they would not be able to overcome their gluttonous feeding habits.

I have called this operation a tubular gastric plication. It converts the stomach from an upside down bota bag into sort of a sausage. It has the advantages, or course, of not being invasive of the gastrointestinal tract. It avoids the sort of gastroplasty features that Dr. Mason showed were not satisfactory for weight loss a number of years ago. Conceivably, it is reversible, at least when the Teflon mesh is used.

Dr. Henry Buchwald (Minneapolis, Minnesota): I believe we are entering a difficult area for jejunoileal and gastric bypass for obesity. We are now seeing the late complications of jejunoileal bypass, and we will in future years see the complications of gastric bypass.

In assessing bypass operations we must remember: 1) Morbid obesity is a disease of unknown etiology. 2) All surgical treatment today is an approximation with reality, since none of the gastrointestinal procedures deal with the unknown etiology of obesity.

Marked obesity is a serious and lethal problem. It is associated with an increased incidence of heart attacks, strokes, hypertension, diabetes, arthritis, pulmonary insufficiency, cholelithiasis, cirrhosis, thrombophlebitis, pulmonary emboli, low back syndrome and disk disease, carcinoma of the uterus and carcinoma of the breast. Drenick has calculated that only one of seven persons with morbid obesity will reach their life expectancy. Furthermore, the disease is a serious psychological, social and economic problem in our society. We are not doing cosmetic surgery; we are performing medical treatment.

All nonmedical treatment for morbid obesity has been documented to have a 99% failure rate. Thus, in constructing a cost/benefit ratio for jejunoileal bypass, one must include, as we do in the treatment of all malignant diseases, the outcome of no therapy and non-operative therapy. Weight loss and satisfaction alone cannot be matched against complications, but the documented decrease in blood pressure, mitigation of diabetes, relief of pulmonary insufficiency, lipid reduction, relief of disk disease and traumatic arthritis, reduced incidence of thrombophlebitis and pulmonary embolization, decreased risk of carcinoma of the uterus and breast and decreased risk of strokes or myocardial infarction must.

I would suggest, therefore, to Dr. Ravitch and others that these factors be weighed strongly in a cost/benefit analysis.

In our own series of approximately 800 patients with jejunoileal bypass, utilizing a 40 cm jejunum to 4 cm ileum, end-to-end anastomosis, Dr. Richard L. Varco and I have seen an excellent weight response and far fewer complications than have been reported by Dr. Ravitch. Our serious complication rate is well under 10%.

For example, our wound infection rate is approximately 2%, and the long-term complications can, for the most part, be avoided by good prophylactic care.

I would like to turn briefly to the paper of Pace and associates. To start, let me state that we have done approximately 100 gastric bypass procedures, with no deaths, one wound infection and overall good results. We are, therefore, not against gastric bypass, gastroplasty or gastric partitioning. I would agree, however, with the authors that 15 patients followed for one year are insufficient for a data base from which to draw a judgment. In the future assessment of gastric procedures, we must be cognizant of late complications. I predict that the staple line will disrupt in the future—late, not early, in some cases, that the orifice will widen and that we will certainly see a failure rate beyond that reported at this time.

Therefore, I will close by pleading for patience and not prematurity in judging all bypass procedures for obesity and in attempting to select a particular preferential operation.

Dr. Hastings K. Wright (New Haven, Connecticut): I rise to insert one more nail in the coffin being constructed by Dr. Ravitch for the jejunoileal bypass.

The gastric stapling procedure obviously produces weight loss by preventing calorie intake. What about intestinal bypass itself? It was supposed to be the best of all possible worlds. The glutton could continue to eat to his heart's desire, and all those excess calories would be swept away in the stool. Is this really true?

We set out to document this malabsorption in three of our own jejunoileal bypass patients by placing them on a 2500 calorie diet. This is a calorie intake which if absorbed will not allow weight loss in a normal person, and one which our patients claimed they were taking.

We studied the patients at four, eight, 12 and 24 months after bypass. To our surprise, at four months, when weight loss as shown by Dr. Scott is at its greatest, we found an average of only about 500 calories per day in the stool. This is significant clinical steatorrhea but insufficient to account for the weight loss documented in our own patients. Similar calorie losses in the stool were documented at 12 and 24 months, when weight was beginning to actually stabilize. These patients could have been losing weight only because they were eating much less than they claimed.

Calorie intact studies of these patients on *ad libitum* diets, not the 2500 calorie study diet, confirmed the conclusion that we had made from the metabolic studies. Patients with intestinal bypasses lose weight because they don't eat.

Dr. Ravitch has talked about the symptoms they get. Our patients tell us they become uncomfortable when they eat, as do the patients with gastric partitioning. If this is so, what advantage is left for the jejunoileal bypass over the Pace procedure?

Dr. Edward E. Mason (Iowa City, Iowa): (slide) The weight loss for our 1971 gastroplasty patients without conversion was about 25 kg at five years. For those that had a second operation to convert them to a gastric bypass, there was little improvement. This was because we did not make the upper part of the stomach smaller. The patients who were operated upon between 1975 and 1978 who had measured small pouches have had an average one year weight loss of 45 kg.

(slide) We are working with three different operations now: the gastroplasty, which we are performing with the opening between pouches on the greater curvature, the gastric bypass with a loop and the gastric bypass with the Roux-en-Y. There are certain things now that have become more precise in gastric bypass and gastroplasty. Dr. Wangensteen's book *Rise of Surgery, from Empiric Craft to Scientific Discipline* seems to be recapitulated by our experience with this operation. There must be a small upper stomach, less than 50 ml, a small outlet 12 mm in diameter and some method of keeping the small outlet from stretching. There must also be some way to keep the staple line from disrupting.

We are using two TA 90 cartridges now, taking three staples out at the greater curvature end of the first cartridge and five from the second. A 0 chromic catgut suture is placed through the wall of the stomach at the end of the staple line and tied down around the greater curvature with a No. 28 French Hurst dilator in place to calibrate the stoma.

The inverted stomach is then reinforced with a 3-0 Proline seromuscular circumferential suture to help control the size of the stoma for as long as that suture will stay in place.

(slide) This is the gastroplasty that failed in 1971. It is obvious why it failed. The upper part of the stomach was too large. There was nothing to keep the stoma from stretching.

My concerns in regard to the technique presented by Dr. Pace are the failure to measure routinely the upper segment volume, the risk of staples pulling through and a stretching of the anterior and posterior wall of the stomach, allowing the stoma to become too large.

Dr. Jonathan E. Rhoads (Philadelphia, Pennsylvania): Some years after Dr. Dragstedt's study of lipocaic, I became involved in a canine study of the changes in the liver following pancreatectomy, and their prevention by giving the dogs an acid alcohol extract of pancreas developed by the Merke, Sharp, & Dohme group. Related studies by the late Paul Gyorgy and associates showed that enzymes in the extract were activated in the small bowel, so that it freed methionine from food protein, thus permitting the body to synthesize choline, which is needed to prevent fatty livers.

In the belief that the short transit times after jejunoileal bypass might prevent adequate methionine release and absorption, I have given the patients 3–6 g of methionine per day and have so far not observed any hepatic complications. The material is quite inexpensive and easy to take. It needs further experimentation, but I think it may be a preventive.

Dr. Mark M. Ravitch (Closing discussion): Dr. Brolin and I are grateful for the attention our effort has received, and I assume that it is because of the intrinsic interest of the subject, rather than the size of our experience or the message which we carry.

This story began in a room like this before this Association some 20 years ago, with a paper of Dr. Arnold Kremen demonstrating that in dogs controlled malabsorption could produce weight loss and was compatible with long survival periods. At that meeting, an increasingly smaller number of you will remember that Dr. Phillip Sandblom rose to say "Yes, there is a doctor in Sweden who had done just exactly this on a patient to lose weight," and Dr. Arnold Kremen got up and said: "I was hoping nobody would mention that, but as long as it has been mentioned we've done one too," and this thing has mushroomed ever since.

We are all grateful for the pioneer studies and the long efforts of Dr. Payne and for the enormously detailed and careful scientific and methodologic studies of Dr. Scott and Drs. Buckwald and Varco. Those studies were what persuaded us, somewhat reluctantly, that we ought to undertake this problem for what has been correctly described as an otherwise unsolvable problem.

I think it is perfectly fair, though I hate to say it, and I don't believe it is necessary to repeat to this audience, as cerebral as we think we are, that, basically surgery—certainly operative surgery—is the application of mechanical principles to disease. We can accept it as axiomatic that any disease which is basically not mechanical in origin will ultimately not be treated mechanically.

Some of our most brilliant successes for a time in the history of surgery have been with mechanical procedures for nonmechanical problems, but I do not believe, in the end, vagotomy, gastrectomy, antrectomy, or any of those things, for example, are going to be the right answer to the ulcer problem. The physiologic answer ought to be; it is that the physiologists are not smart enough to arrive at that.

I must say I appreciate any support I can get anywhere, and I appreciate Dr. Wright's support since we have been enormously impressed by his work on absorption and malabsorption. My aim is to drive home "a nail in this coffin," and our abstract ends with a question. The question is: Is the game worth the candle?

For me, right now, I find that I am not able to schedule patients for a jejunoileal shunt, and it may be that I cannot face their problems as well as they can face them.

May I comment on Dr. Pace's nice paper with just one slide? We created some gastric bypasses in dogs 15 years ago (slide) and, in essence, closed off the stomach and did a gastroenterostomy around it. We found that precisely because the staples are not necrotizing instruments and the pressure is not destructive, the mucosa stays intact. It does not heal mucosa to mucosa in the undivided viscus, some of the staples tear out.

What the long-term balance will be I don't know. It is perfectly possible that enough of the staples will stay behind to maintain the reduced weight after it has been achieved. This is an interesting attempt, and somthing needs to be done for these people.

DR. LARRY C. CAREY (Closing discussion): Morbid obesity presently holds a position similar to that of alcohol 20 years ago. A perception that the problem is simply a matter of character weakness is improper. Morbid obesity, like alcoholism, is a disease which leads to other diseases.

The surgical treatment of morbid obesity, much like the surgical treatment of the complications of alcoholism, is a treatment of symptoms, and not the disease. We don't understand the disease, and it ultimately will not have a surgical solution, but until we understand it better, we have, I believe, a responsible role to play in the treatment of the symptoms.

Jejunoileal bypass is the standard against which all other surgical procedures for this symptom must be compared. Now, I have, in common with Dr. Payne, a lack of experience. He has done no gastric bypasses, and I have done no jejunoileal bypasses, so we share that vacancy in experience. I suspect I will not do any jejunoileal bypasses because of the ravages of the problem that I have been witness to in following the patients that have been done by others.

Gastric partitioning will very likely not provide the ultimate solution, but it seems to be a logical step in the evolution of the surgical treatment for this disease.

Gastric Partitioning for Morbid Obesity

WILLIAM G. PACE, M.D., EDWARD W. MARTIN, JR., M.D., TED TETIRICK, M.D., PETER J. FABRI, M.D.,
LARRY C. CAREY, M.D.

The complication rate in jejunoileal bypass for morbid obesity is unacceptably high. Gastric bypass is technically difficult. In our series, 115 patients have undergone gastric partitioning for morbid obesity. The operation consists of stapling across the stomach below the gastroesophageal junction, leaving a gastric food reservoir of 50–60 cc. A 1 cm opening is left in the central portion of the staple line, allowing slow emptying into the distal stomach. The result is a reduced eating capacity and frequency which produce loss in weight. Three-quarters of the patients are women, and the age range is 17–62 years. Preoperative weights averaged 147 kg. Mean operative time was 48 minutes, and postoperative stay was 6.2 days. All patients were extensively evaluated preoperatively with upper GI series, cholecystogram, a number of blood chemistry tests, and endocrinologic and psychiatric consultations. All patients underwent a preoperative Minnesota Multiphasic Personality Inventory test. Cholecystectomy for cholelithiasis was performed on 18% of the patients at the time of operation. Of the seven patients operated on more than one year ago, five have lost an average of 31.6% of their preoperative weight. Of the 12 operated on less than one year but more than six months ago, eight have lost an average of 21% of their initial weight. The early failure rate of 33% has been reduced to 15% at present. One death occurred from pulmonary embolus 10 days following discharge, giving a mortality rate of .08%. The complication rate is 10%, comprising two pulmonary emboli, two psychoses, one wound dehiscence, one wound hernia, and ten wound infections, six of which were minor. There have been no complications of ulcer disease, reflux esophagitis, liver disease, renal disease, or metabolic disorders. Gastric partitioning is a safe, fast effective alternative for the surgical treatment of morbid obesity.

From The Department of Surgery,
The Ohio State University Hospitals,
Columbus, Ohio

SURGICAL TREATMENT of morbid obesity is recognized as a crisis-oriented mode of therapy and is universally regarded as a last effort after complete failure of all other attempts at weight control. At the same time, because medical and psychiatric programs have a discouragingly low success rate, morbidly obese patients are almost certainly condemned to a life of indolence, nonproductivity and often support by state, county and city welfare agencies. Attention given this problem should be no less than that directed to other self-inflicted diseases, such as cirrhosis, carcinoma of the lung and certain types of atherosclerotic disease.

The literature is replete with suggestions for surgical procedures to control the ingestion of food, but no data have been reported concerning the stapled gastric anastomosis. A safe, reproducible, rapid method of gastric partitioning is described. Simultaneous creation of a small gastric pouch and a standard 9 mm conduit into the distal gastric remnant is accomplished. The gastric conduit is always exactly the same size without need for calibration if details of the technique are scrupulously observed. The stapled gastric anastomosis heals within eight weeks. Patient cooperation is essential during the postoperative period, and this is most successfully secured by a team approach by the physician, the psychiatrist, the dietician and the nurse.

Experimental Design

Use of the Autosuture® TA55 and TA90 devices was investigated for construction of a gastric partition in experimental animals. The commercially available sterile staple cartridges contain two parallel rows of stainless steel staples. The 4.8-mm staples were used to construct a gastric pouch. Opposite the space between adjacent staples in one row, there is a staple in the parallel row. Removing three staples, two from the proximal row and the interposed staple from the distal row fashions a 9 mm defect in the double row of staples (Fig. 1). When the remaining staples in the cartridge are applied across the stomach, the defect in the staple line allows the passage of a 9 mm bougie or a No. 18 F Salem sump tube from the proximal pouch to the distal stomach.

Variations of staple removal before application to cadaver and canine stomachs demonstrated that the removal of two staples resulted in a small diagonal defect which tended to behave as a flap valve, while the removal of four or more staples resulted in a defect which was too large. Since staple cartridges with missing staples were not commercially available, the TA55 and TA90 4.8 mm cartridges were modified: first, the staples were partially discharged to expose the points; then fine hemostats were used to remove the three staples. It was then necessary to replace the remaining staples very carefully in order to avoid damage to the tiny staple shafts. Because it became clear that the

---

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

0003-4932/79/0900/0392 $00.95 © J. B. Lippincott Company

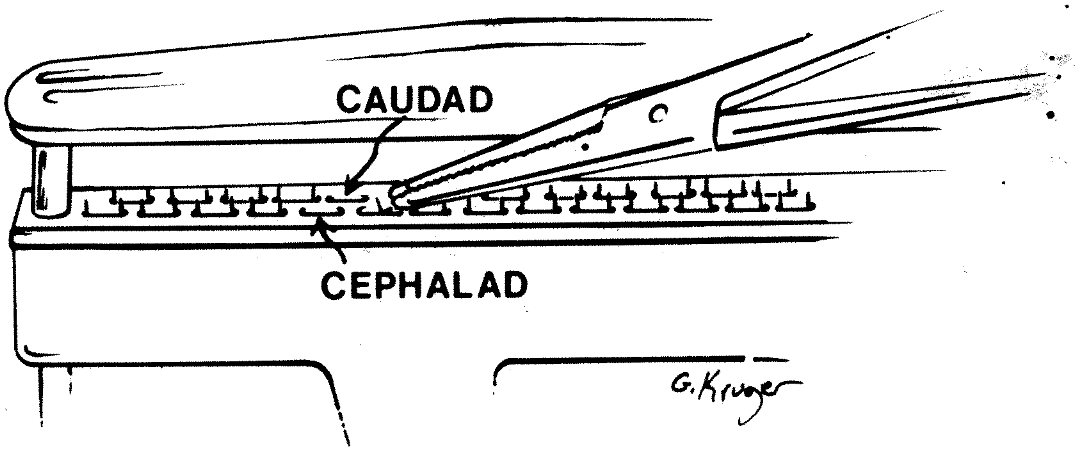


FIG. 1. Removal of three staples from TA90 cartridge.

staples could not be replaced into the cartridge without damage, the approach to staple removal was reversed. The pusher bars on the back of the cartridge were first removed by using the point of a hemostat between the bar and the plastic back of the staple cartridge. By spreading the points of the hemostat, each bar can be slowly and carefully extracted. Displacement of the three staples is then accomplished by pushing them out with the blunt end of a Keith needle. The pusher bars are then carefully repositioned, and the cartridge placed in the Autosuture device.

Repeated measurements in the cadaver and canine stomachs clearly demonstrated that the one most important aspect of accurate calibration was avoidance of "bunching" of the stomach in the clamp. As the wing nut of the stapling device is tightened, it is absolutely imperative that the stomach, which increases in transverse dimension as it is compressed, not be allowed to come into simultaneous contact with the pin and the connecting bar at the opposite (closed) end of the jaws of the stapling device. In every instance in which this precaution was not taken, the stomach was "bunched" or compressed from the greater to the lesser curvature, and the opened specimen could then be stretched to allow passage of a bougie larger than 9 mm through the stoma.

The procedure was carried out in ten standard breed foxhound dogs. There was no mortality, and no morbidity occurred in the 18 month follow-up period. All the animals were carefully observed with endoscopy, radiography, measurements of acid secretion, responses to test meals and hormonal studies including gastrin, GIP and VIP levels. There were no significant changes in any of these parameters, and no gastric or duodenal ulceration occurred.

Clinical Material and Methods

Morbidly obese patients were first treated with gastric partitioning in June 1977. Multiple measurements of acid values in the proximal gastric pouches of these patients have paralleled the results of animal experiments in demonstrating a lack of significant acidity even in response to pentagastrin stimulation.[5]

Selection of patients followed the guidelines of Mason et al.,[6] Payne, Scott and others. Morbid obesity has been well defined. All patients were at least twice normal weight by actuarial standards or more than 100 lbs. overweight and had failed to lose weight by all nonsurgical methods. Preoperative evaluation included upper and lower gastrointestinal roentgenograms, cholecystography, intravenous pyelography, complete endocrine, gastrointestinal and cardiologic evaluation and evaluation of liver and renal function. A serious effort was made through preoperative psychiatric evaluation to select patients who could reasonably tolerate a lifetime of restricted oral intake.

Technique

Balanced general anesthesia with endotracheal intubation is used. An incision from xiphoid to umbilicus is adequate for exposure, and retraction is facilitated by use of the "upper hand" retractor, using a modified blade to retract the xiphoid superiorly and a self-retaining Balfour-type retractor for the rectus muscles. After a thorough general intra-abdominal exploration, the thick fat left lobe of the liver is retracted superiorly without cutting the triangular ligament, and the cardia of the stomach is visualized just below the cardioesophageal junction. The spleen is not disturbed, and none of the vasa brevia are divided. With blunt dissection, using the indwelling endogastric Salem sump tube for guidance, the index finger is passed around the stomach from greater to lesser curvature, taking care to pass in front of the posterior vagus nerve. The thumb is passed around the lesser curvature to meet the index finger, passing between the anterior vagus and the anterior wall of the stomach. The left index finger is then passed around this passage-

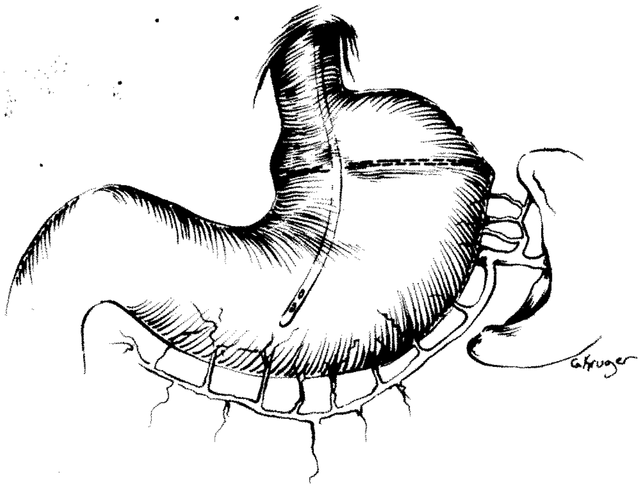


FIG. 2. Isolation of nerve of Latarjet and placement of TA90 above vasa brevia.

way, going from lesser to greater curve of the stomach, and is used to guide the lower jaw of the TA55 or TA90 stapler around the stomach (Fig. 2).

The appropriate pin is then put into place, and the anesthesiologist is asked to withdraw the nasogastric tube until it lies within the esophagus, well away from the jaws of the stapling device. The wing nut of the device is then tightened, taking extreme care to avoid "bunching." If the stomach fills the entire jaw area of the stapling device, the wing nut is loosened and the device is repositioned nearer the esophagogastric junction. Only when the operator is certain that the stomach does not completely fill the jaws is the wing nut completely tightened, and the staples are discharged.

At this point, the nasogastric tube may be pushed back into the small proximal gastric pouch, and the pouch is filled with saline by the anesthesiologist if calibration is desired. If the clamp has been properly placed without "bunching" of the stomach, the pouch will hold no more than 30–45 cc when the TA55 has been used and no more than 30–60 cc when the TA90 has been used. The TA55 must be used with extreme care, because although the device is technically much easier to apply in a grossly obese patient, it is very easy to "bunch" the stomach, and the resulting stoma will be too large for effective weight reduction.

The pin is then removed from the stapling device, and the device removed. The nasogastric tube is readvanced by the anesthesiologist, the operator carefully guiding it through the opening into the distal gastric pouch. The tube is taped to the patient's nose and left in place for four days postoperatively. Although in the canine and cadaver stomachs it was noted that the gastric mucosa is fractured along the entire line of compression by the stapling device and muscularis is stapled to muscularis, the presence of the nasogastric tube through the stoma has apparently been adequate to prevent mucosal reapproximation and healing with obstruction, even though in several instances the tube was pulled by the patient in the recovery room within four hours of operation.

A liver biopsy is taken, and the fascia is closed in a single layer. The subcutaneous tissue is carefully irrigated, hemostasis is secured, and the skin is closed with a stapling device without drainage or suction.

Postoperative Management

While the technical aspect of the gastric partitioning operation is simple, the postoperative management is extremely difficult and important. All patients are given miniheparin, 5000 units every eight hours, beginning before operation and continued until discharge from the hospital. Patients' beds are equipped with overhead trapeze bars, and patients are required to become ambulatory on the night of operation. Vigorous attention is paid to the tracheobronchial toilet. Nothing is given by mouth for five days, then clear liquids are given. The water glass at the bedside is replaced by small, disposable 1-oz. plastic medicine cups, and patients are warned that one of these cups represents the size of the gastric pouch and that no more than that quantity of fluid may be taken at one time.

At this point, it is imperative that a team approach to the care of the postoperative patient be initiated, utilizing the dietitian, psychologist, nursing staff and physician.

It is imperative that the patient be instructed not to challenge the stapled suture line with large quantities of fluid or with solid food until after the eighth postoperative week. Tensometer studies performed in the Battelle Laboratories in animal models in which disruption of the stapled gastric suture lines was deliberate demonstrated that weakness of the stapled suture lines persisted for approximately two weeks, after which strength increased to a maximum, exceeding the strength of the surrounding gastric wall, approximately eight weeks after operation. It is equally essential to instruct these patients concerning the thorough mastication of food. They must be told not to eat any food, even if it has been prepared in a blender, unless it has first been forced through a strainer. Failure to follow either of these warnings absolutely will invariably result in an experience of severe, burning left subcostal pain, along with esophageal pain, usually nausea and sweating, often wretching and vomiting and inevitable disruption of the staple line and failure of the procedure.

At the time of discharge, the patient is thoroughly instructed concerning the liquid diet which is to be fol-

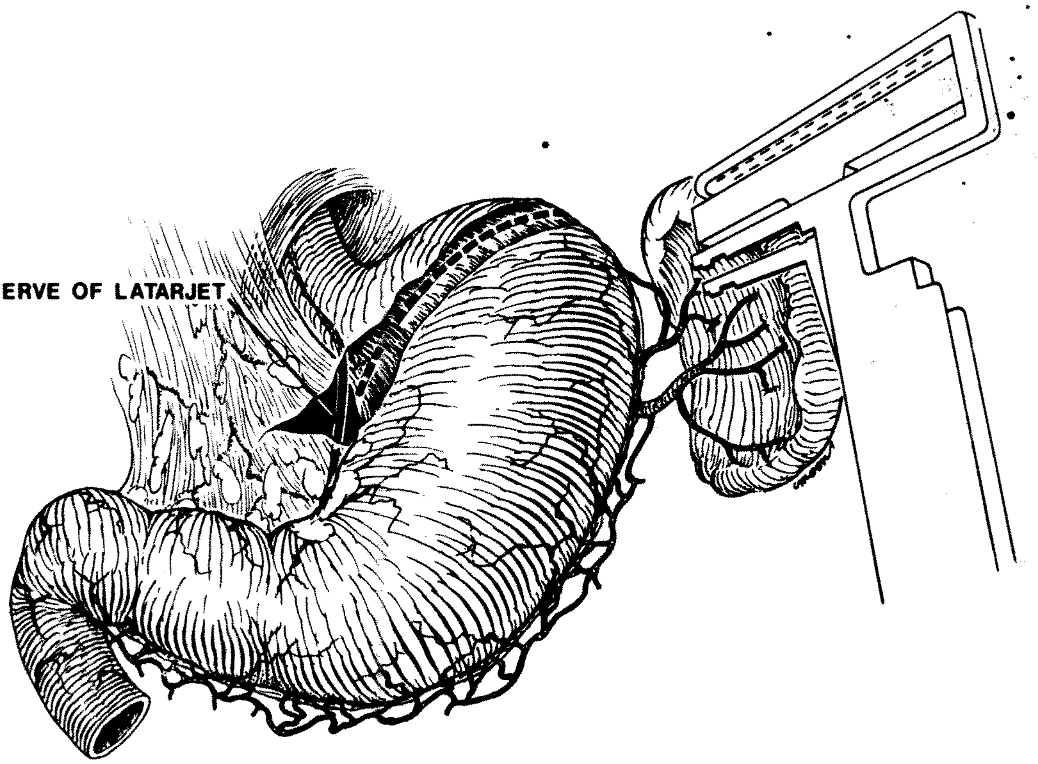


FIG. 3. Completed TA90 staple partition.

lowed for eight weeks. The first follow-up visit is arranged at two weeks, with subsequent visits monthly. The patient is given a telephone number at which one member of the team is available during the 24 hours for assistance. At periodic visits the patient's weight is carefully checked, and problems are discussed by the dietitian, the physician and the psychiatrist or psychologist.

Results

During the past 21 months, gastric staple partitioning has been performed on 220 patients, 56 men and 174 women, ranging in age from 17 to 63 years, with a mean age of 39. The average preoperative weight was 290 pounds. The only death (rate of 0.4%) resulted from a pulmonary embolus ten days after discharge from the hospital; 11 patients (5%) had postoperative complications which prolonged the hospital stay. Complications included two stomal obstructions, one pulmonary embolus, two fistulas, one partial staple line necrosis with leak, four severe wound infections and two dehiscences. Associated major technical problems included two splenectomies and two posterior lacerations of the stomach, one of which occured with a reoperation for a failed partition. There was one misplaced staple line. Seven of the 11 major complications were treated with total parenteral nutrition (TPN) (Table 1).

Of the 220 patients, 180 are considered to have successful results (82%), while 40 are considered failures (18%). Criteria for success include continued weight loss of at least 5 lbs./month and continued rapid satiety. All of the patients in the failure group have been carefully questioned, and it is clear that in every instance there was early ingestion of solid food or of large quantities of liquid. Almost without exception, the patient could pinpoint the exact moment of disruption of the partition. Although over half the patients considered successful have had a very short follow-up, this period coincides with that during which patients have been advised of the dietary restrictions necessary to assure adequate healing of the gastric staple line.

Eight patients have undergone partitioning concurrent with restoration of a jejunoileal bypass necessitated by metabolic problems. Two gastric bypass operations were restored, and partitioning carried out.

Weight trends for each three month period are illustrated in Table 2. Sixteen of the 40 patients con-

TABLE 1. *Two hundred-twenty Gastric Partitioning Procedures: Major Complications (11 Patients)*

Complication	% All Patients
Wound infection	4.5
Psychosis	1.4
Dehiscence	1.0
Hernia	1.0
Pulmonary embolus	1.0
Death	1.4

TABLE 2. *Weight Trends in 220 Gastric Partitioning Procedures*

Months Postop.	Patients	Failures	Average Weight Loss
1–4	119	2 (1.7%)	25 pounds
4–6	63	22 (35%)	45 pounds
6–12	27	12 (44%)	70 pounds
12–18	9	4 (44%)	98 pounds
18 plus	2	0	110 pounds
Total	220	40* (18%)	

* 16 of these patients have undergone restapling.

sidered to be failures have now had a second partitioning procedure without mortality. Subtracting these 16 patients from the group of 40 leaves only 24 patients with unsatisfactory weight loss (11%). Longer follow-up will be necessary to assess the true effectiveness of gastric partitioning.

Discussion

Any surgical approach to the control of morbid obesity must concern two aspects: the risk to the patient and the safety of the procedure. The surgical treatment of morbid obesity is an entirely elective procedure; therefore, ideally, the patient should be more at risk from the secondary effects of obesity than from the technical procedure and its possible complications. Surgical attempts at weight control must be directed into one of four avenues—central nervous system modification or manipulation to control appetite centers, surgical removal of excessive adipose tissue, surgical reduction of the available absorptive surface of the intestinal tract or construction of physical restrictions to the volume of caloric intake. Each of these approaches has been reviewed exhaustively in the literature, and it is clear that there is no completely safe and totally reliable surgical solution to the problem of weight control.

Neurosurgical or neurotoxic approaches to the establishment of a controllable analogue of anorexia nervosa as well as other approaches to control of an appetite center have been unproductive, although this would appear to be the ideal approach. Hypothalamic lesions in laboratory animals have been effective but cannot be reliably created and are not suitable for clinical application.

Weight reduction through lipectomy or panniculectomy carries a high degree of risk and is always followed by immediate replacement.

Modifications of the intestinal absorptive surface have been extensively investigated in laboratory and clinical applications. The most acceptable clinical approach appears to be a modification of the jejunoileal bypass. Although the technical procedure is simple, the multiple and severe short- and long-term complications of this procedure have led to its abandonment by most surgeons.[2] While a few reports of large numbers of apparently successful cases of jejunoileal bypass still support the concept, the problems of quality of life, degree of weight loss, standardization of the procedure, the necessity for reoperation and revision and even an inquiry into the cost effectiveness of this operation all tend to condemn it.

Surgical attempts to control caloric intake were first made by means of mandibular fixation. While this procedure is effective temporarily, there is no long-term modification of eating habits or behavior. Long-term sociologic acceptance is negative, and removal of the fixation wires is followed by a 100% weight return.

The gastric bypass procedures, pioneered and extensively studied by Mason and others, involve the establishment of a new, small gastric pouch proximally, total or subtotal exclusion of the remainder of the distal stomach and the establishment of a calibrated small outlet or stoma from the small proximal pouch into the small bowel or into the distal excluded stomach by way of a gastrogastrostomy[3] or a small calibrated "pseudopylorus."

The automatic suturing devices have greatly facilitated the total partitioning of the stomach without the necessity for total division of the stomach. Unfortunately, the subsequent gastrogastrostomy or gastroenterostomy is technically exacting, the calibration of the stoma is difficult and subject to individual variation, mobilization of the spleen carries a risk, and the required enterotomies result in potential wound contamination. Mason attempted to simplify the procedure by performing a subtotal division of the stomach from the lesser to the greater curvature for calibration.[1] The failures in this group of patients resulted from stretching of the residual gastric tube. Gomez attempted to prevent this stretching by the application of four rows of staples from lesser to greater curvature and then reinforcing the area of tube passage with nonabsorbable sutures to create a "pseudopylorus" which would presumably be difficult if not impossible to distend. Although this latter procedure is the first which does not involve an enterotomy, a difficult mobilization of the stomach is still required, and complications have been reported.

In an attempt to further simplify and improve the safety of the gastric bypass, the first consideration was given to the problem of calibration of the stoma or outlet of the proximal gastric pouch. The extensive attention given this aspect of the operation in the literature attests to the inadequacy of a good standardizing procedure. The suturing device itself seemed ideally suited to the solution of the problem. Closure of the device on the cadaver or the canine stomach effects maximum compression of the muscularis with actual fracture of the mucosa. The muscularis in this degree of compression cannot be further distracted by traction in a transverse direction; therefore, application of the staples at this point attach muscularis to muscularis, and the defect permitted by the removal of three of the staples cannot be further stretched. The resulting defect exactly permits the passage of a 9 mm bougie in every instance and affords a solution to the problem of calibration.

The pouch size is determined by the location of the clamp on the transverse body of the stomach and has been recommended to be optimal at 50 cc by Mason and others.[6] In actual practice, any attempt to construct a larger pouch will result in attempting to staple an area of the stomach which exceeds 90 mm in greatest stretched transverse dimension and will inevitably result in "bunching" at the staple line and eventually in dilation of the stoma, despite the most careful postoperative follow-up.

There is still a high risk of failure of stoma calibration with use of the TA55 device. There is a strong tendency to place the device too far distal to the esophagogastric junction, resulting in "bunching" of the stomach. Although the TA90 is much more cumbersome to use, it is probably the safer in preventing stomal distention. Furthermore, the very tiny reservoir resulting from proper placement of the TA55 may in the long-term be incompatible with an acceptable quality of life for the patient.

None of the other approaches to gastric bypass adequately address the problem of postoperative supportive management of this group of very difficult patients. Even superficial interrogation clearly indicates that they not only consume prodigious quantities of food but that they usually do so without significant mastication and with great speed. In this study, it was clear that a single application of the Autosuture device with two rows of staples appeared to be a very fragile mechanical barrier to a bolus of food.

Others have attempted to solve this problem with double applications involving four rows of staples or with reinforcing sutures, but no one suggested limitation of intake to a clear liquid diet of limited quantity. Yet, the tissue healing curves for stapled dog stomach in this laboratory demonstrated clearly that the staple line would probably be disrupted by a severe challenge prior to the eight week healing time. Indeed, interview of all failures in this series has conclusively shown that each failure could be exactly pinpointed to a single episode of early ingestion of solid food. In the early phases of this study, this was viewed as a coincidence, but since the establishment of the team concept with increased reinforcement of restrictions, the failure rate has decreased significantly.

While there have been multiple suggestions for increasing the numbers of staples or doubling the suture rows or adding reinforcing sutures of some nonabsorbable type in the partitioning procedure, it appears that all these precautions are unnecessary if the total cooperation of the patient can be secured. While others[3] have reported late disruption of a stapled partition following gastrogastrostomy, it is probably that the disruption resulted from early ingestion of solid food which overdistended the gastric pouch and placed excessive stress on the stapled suture line before the eight week healing period. There have been no disruptions or failures in this series after the eight week healing of the stoma and staple partition.

Conclusions

A modification of the gastric bypass using the presently available Autosuture devices with a modification of the staple cartridge by removal of three of the staples has been investigated in the laboratory and in morbidly obese patients. The device is used to partition the stomach, creating in one application of staples a small proximal gastric reservoir, a small calibrated conduit, and a large distal gastric pouch. The procedure is safe, rapid and technically relatively simple, but a successful outcome depends upon proper selection of patients and the absolute cooperation of the patients in the postoperative period to permit healing of the staple anastomosis. While the long-term effects cannot be predicted, short-term laboratory follow-up has suggested that these are minimal and should certainly not differ significantly from those which could result from other forms of the gastric bypass.

Although this modification is a technically simple procedure, careful attention must be given the placement of the suturing device to avoid "bunching" of the stomach, which will inevitably result in long-term stretching of the internal stoma as the full transverse dimension of the stomach is re-established.

References

1. Buchwald, H. and Varco, R. L.: Metabolic Surgery. New York, Grune & Stratton, p. 42, 1978.
2. Conference on Obesity. Washington, DC, National Institutes of Health, December 1978.
3. LaFave, J. H. and Alden, J. F.: Gastric Bypass in the Operative Revision of the Failed Jejunoileal Bypass. Arch. Surg., 114:438, 1979.
4. Mason, E. E. and Ito, C.: Gastric Bypass in Obesity. Surg. Clin. North Am., 47:1345, 1967.
5. Mason, E. E., Munns, J. R., Kealey, G. P. et al.: Effect of Gastric Bypass on Gastric Secretion. Am. J. Surg., 131:162, 1976.
6. Mason, E. E., Printen, K. J., Hartford, C. E. and Boyd, W. C.: Optimizing Results of Gastric Bypass. Ann. Surg., 182:405, 1975.

DISCUSSION

DR. J. HOWARD PAYNE, SR. (Los Angeles, California): A search of the literature showed innumerable publications on the various surgical approaches to the morbidly obese patient since 1965. Our first experience was in 1956, but our first publication was not until 1963. It took us seven years to arrive at the conclusion that the jejunocolic bypass was hazardous and should be abandoned. We now have 23 years of experience with the surgical approach to hyperobesity. We still see and follow our first patient to undergo surgical therapy for malnutrition morbid obesity. Every effort has been made to provide for the patient's long-term care, clinical observation and problems. With this background, we have periodically reported our results to provide a perspective for other investigators, with our approach, and to the adventuresome who are trying other surgical methods to reduce weight.

The bypass with the end-to-end anastomosis, known as the Scott procedure, decompresses the bypassed bowel into the colon. There will be regurgitation of large bowel content into the bypassed bowel whether the ileocolic anastomosis is into the cecum, transverse colon or sigmoid. In may opinion, this is the primary cause of one of the relatively new problems, namely, the so-called bypass enteritis syndrome. These problems are responsible for many revisions and takedown operations. One patient has described the syndrome as "the bloats and the blahs."

The gastric bypass has been changed so many times that I cannot keep up with it. It is inappropriate to draw conclusions with only one year of follow-up study. We are now seeing failures and devastating complications. I have never done a gastric bypass but have consulted with patients and their doctors relative to the procedure and their problems. These data could supply enough information for a separate manuscript. The use of large stapling devices in the upper abdomen in a 400 pound patient is difficult and uncertain. The most skilled surgeons have problems maneuvering in the subdiaphragmatic area of the celomic cavity even in the patient who is not obese.

With the foregoing in mind plus many happy alumni, we have continued to do the jejunoileal bypass using 35 cm of proximal jejunum anastomosed end-to-side to the distal 10 cm of the ileum with a minor modification designed to prevent reflux into the bypassed segment. This procedure has been named by others as the Payne procedure. We have classified our results: excellent, 65%; satisfactory, 25% and failures, 10%. I do not use the stapling machine.

It is imperative that patients selected for this operation continue to meet the original strict criteria. Some form of surgical procedure appears to be the only method of weight reduction that does not depend on impractical and dietary restrictions. Unfortunately, too many of these operations are being done on poorly selected patients by surgeons who are not fully aware of all the pre- and postoperative problems.

I do not agree with the authors' conclusions. I do think that appropriate investigations should be continued. The results are worthwhile in spite of the costs.

DR. H. WILLIAM SCOTT, JR. (Nashville, Tennessee): I will comment predominantly on the experience that we have had from 1966 through 1978 with 225 massively obese patients who underwent jejunoileal bypass.

(slide) The slide shows findings in addition to obesity in these 225 patients, and you will note that hyperlipidemia occurred in 112 patients, 62 had gallstones; 39, diabetes; 31, diastolic hypertension, and so on.

The early postoperative mortality was 2%.

(slide) This slide shows the changes in body weight in four study groups based on different dimensions of jejunoileal bypass, and the curves of the mean change from 100%, representing original preoperative weight plotted against time. The greatest sustained weight reduction occurred in patients who had total incontinuity small intestine shortened to 45–50 cm.

The early postoperative complications, such as wound seroma, wound infection and thrombophlebitis, which Dr. Ravitch has detailed, were quite similar in our group, and occurred in 22%. Prophylactic efforts, however, have almost eliminated these surgical complications in the last 100 patients.

Major metabolic complications include oxalate urinary stones in 15% and episodes of the enterohepatic syndrome of hepatocellular injury in 12% of patients. There were four late deaths of liver failure.

We have learned from patient studies, from animal models, and the work of others, that the hyperoxaluria and urinary stones result from the short bowel, and not from the bypassed gut. All patients are currently instructed prior to discharge and repeatedly during follow-up studies to follow a high protein, low fat, low oxalate diet, in an effort to reduce the hyperoxaluria and the incidence of oxalate stones.

In contrast, the flu-like syndrome of nausea, vomiting, hypergeusia, myalgias and prostration, accompanied by elevation of liver enzymes and later by icterus and hepatomegaly, reflects hepatocellular injury from absorption of toxic metabolites of heavy bacterial growth in the bypassed small bowel. All patients are taught to recognize these symptoms, and prompt treatment with oral antibiotics—we prefer Flagyl, (micronidazol)—and high protein diet eliminates the symptoms in a few days in most instances. Resistance to these simple measures requires hospitalization for enteral or parenteral hyperalimentation and more potent antibiotics, and, if necessary, takedown of the bypass.

Metabolic benefits include mean weight loss of 45–50%, reduction in serum cholesterol and triglyceride level of 40–60%, and uniform relief of adult onset diabetes.

(slide) These show the changes in a group of 71 patients who had Frederickson Type IV hyperlipoproteinemia in this group, preoperative cholesterol plotted in the white bar graph, and triglyceride in the same; and after jejunoileal shunt there was a considerable drop, averaging 40%, in baseline cholesterol, and 50–60% in triglyceride.

(slide) The same in true with familial hypercholesterolemia, plotted here, the baseline just under 300 mg/dl, and the triglycerides elevated in the same range, with a drop of 50%, on the average, in cholesterol level following jejunoileal shunt, a little less regular pattern of drop with the triglyceride.

With current dimensional considerations, good results have been achieved in 75% of our patients. However, certainly morbidity and mortality risks are significant, and I must agree with Dr. Ravitch that these limit wide application of the procedure.

Gastric stapling is indeed an attractive alternative for obese patients who are not hyperlipidemic.

DR. MAX RAYMOND GASPAR (Long Beach, California): I bring to your attention another approach to this problem which was conceived by Dr. Larry Wilkinson, of Albuquerque, with the idea of reducing gastric reservoir capacity. His idea was to plicate the stomach upon itself, and then wrap it with a mesh.

He found in animals that it was necessary to use a mesh to maintain the plication, or the animals would distend the stomach.

At first, this was done by plicating the greater curvature. I have followed Dr. Wilkinson's approach, and we have revised the operation to do a Nissen fundoplication high on the stomach, and then to fold the stomach upon itself below the plication. Dr. Wilkinson wraps the stomach with a Marlex mesh; I have started using a Teflon mesh. We put a Levaculator tube into the stomach to calibrate the size of the stomach at 36 French.

Dr. Wilkinson has operated on 26 patients, the oldest 2½ years ago. He has followed eight patients for more than a year. They have lost an average of 80 lbs. I have operated on seven patients. They have had satisfactory weight loss to date, with no metabolic complications. I have avoided this operation in patients who claim thay they would not be able to overcome their gluttonous feeding habits.

I have called this operation a tubular gastric plication. It converts the stomach from an upside down bota bag into sort of a sausage. It has the advantages, or course, of not being invasive of the gastrointestinal tract. It avoids the sort of gastroplasty features that Dr. Mason showed were not satisfactory for weight loss a number of years ago. Conceivably, it is reversible, at least when the Teflon mesh is used.

Dr. Henry Buchwald (Minneapolis, Minnesota): I believe we are entering a difficult area for jejunoileal and gastric bypass for obesity. We are now seeing the late complications of jejunoileal bypass, and we will in future years see the complications of gastric bypass.

In assessing bypass operations we must remember: 1) Morbid obesity is a disease of unknown etiology. 2) All surgical treatment today is an approximation with reality, since none of the gastrointestinal procedures deal with the unknown etiology of obesity.

Marked obesity is a serious and lethal problem. It is associated with an increased incidence of heart attacks, strokes, hypertension, diabetes, arthritis, pulmonary insufficiency, cholelithiasis, cirrhosis, thrombophlebitis, pulmonary emboli, low back syndrome and disk disease, carcinoma of the uterus and carcinoma of the breast. Drenick has calculated that only one of seven persons with morbid obesity will reach their life expectancy. Furthermore, the disease is a serious psychological, social and economic problem in our society. We are not doing cosmetic surgery; we are performing medical treatment.

All nonmedical treatment for morbid obesity has been documented to have a 99% failure rate. Thus, in constructing a cost/benefit ratio for jejunoileal bypass, one must include, as we do in the treatment of all malignant diseases, the outcome of no therapy and non-operative therapy. Weight loss and satisfaction alone cannot be matched against complications, but the documented decrease in blood pressure, mitigation of diabetes, relief of pulmonary insufficiency, lipid reduction, relief of disk disease and traumatic arthritis, reduced incidence of thrombophlebitis and pulmonary embolization, decreased risk of carcinoma of the uterus and breast and decreased risk of strokes or myocardial infarction must.

I would suggest, therefore, to Dr. Ravitch and others that these factors be weighed strongly in a cost/benefit analysis.

In our own series of approximately 800 patients with jejunoileal bypass, utilizing a 40 cm jejunum to 4 cm ileum, end-to-end anastomosis, Dr. Richard L. Varco and I have seen an excellent weight response and far fewer complications than have been reported by Dr. Ravitch. Our serious complication rate is well under 10%.

For example, our wound infection rate is approximately 2%, and the long-term complications can, for the most part, be avoided by good prophylactic care.

I would like to turn briefly to the paper of Pace and associates. To start, let me state that we have done approximately 100 gastric bypass procedures, with no deaths, one wound infection and overall good results. We are, therefore, not against gastric bypass, gastroplasty or gastric partitioning. I would agree, however, with the authors that 15 patients followed for one year are insufficient for a data base from which to draw a judgment. In the future assessment of gastric procedures, we must be cognizant of late complications. I predict that the staple line will disrupt in the future—late, not early, in some cases, that the orifice will widen and that we will certainly see a failure rate beyond that reported at this time.

Therefore, I will close by pleading for patience and not prematurity in judging all bypass procedures for obesity and in attempting to select a particular preferential operation.

Dr. Hastings K. Wright (New Haven, Connecticut): I rise to insert one more nail in the coffin being constructed by Dr. Ravitch for the jejunoileal bypass.

The gastric stapling procedure obviously produces weight loss by preventing calorie intake. What about intestinal bypass itself? It was supposed to be the best of all possible worlds. The glutton could continue to eat to his heart's desire, and all those excess calories would be swept away in the stool. Is this really true?

We set out to document this malabsorption in three of our own jejunoileal bypass patients by placing them on a 2500 calorie diet. This is a calorie intake which if absorbed will not allow weight loss in a normal person, and one which our patients claimed they were taking.

We studied the patients at four, eight, 12 and 24 months after bypass. To our surprise, at four months, when weight loss as shown by Dr. Scott is at its greatest, we found an average of only about 500 calories per day in the stool. This is significant clinical steatorrhea but insufficient to account for the weight loss documented in our own patients. Similar calorie losses in the stool were documented at 12 and 24 months, when weight was beginning to actually stabilize. These patients could have been losing weight only because they were eating much less than they claimed.

Calorie intact studies of these patients on *ad libitum* diets, not the 2500 calorie study diet, confirmed the conclusion that we had made from the metabolic studies. Patients with intestinal bypasses lose weight because they don't eat.

Dr. Ravitch has talked about the symptoms they get. Our patients tell us they become uncomfortable when they eat, as do the patients with gastric partitioning. If this is so, what advantage is left for the jejunoileal bypass over the Pace procedure?

Dr. Edward E. Mason (Iowa City, Iowa): (slide) The weight loss for our 1971 gastroplasty patients without conversion was about 25 kg at five years. For those that had a second operation to convert them to a gastric bypass, there was little improvement. This was because we did not make the upper part of the stomach smaller. The patients who were operated upon between 1975 and 1978 who had measured small pouches have had an average one year weight loss of 45 kg.

(slide) We are working with three different operations now: the gastroplasty, which we are performing with the opening between pouches on the greater curvature, the gastric bypass with a loop and the gastric bypass with the Roux-en-Y. There are certain things now that have become more precise in gastric bypass and gastroplasty. Dr. Wangensteen's book *Rise of Surgery, from Empiric Craft to Scientific Discipline* seems to be recapitulated by our experience with this operation. There must be a small upper stomach, less than 50 ml, a small outlet 12 mm in diameter and some method of keeping the small outlet from stretching. There must also be some way to keep the staple line from disrupting.

We are using two TA 90 cartridges now, taking three staples out at the greater curvature end of the first cartridge and five from the second. A 0 chromic catgut suture is placed through the wall of the stomach at the end of the staple line and tied down around the greater curvature with a No. 28 French Hurst dilator in place to calibrate the stoma.

The inverted stomach is then reinforced with a 3-0 Proline seromuscular circumferential suture to help control the size of the stoma for as long as that suture will stay in place.

(slide) This is the gastroplasty that failed in 1971. It is obvious why it failed. The upper part of the stomach was too large. There was nothing to keep the stoma from stretching.

My concerns in regard to the technique presented by Dr. Pace are the failure to measure routinely the upper segment volume, the risk of staples pulling through and a stretching of the anterior and posterior wall of the stomach, allowing the stoma to become too large.

Dr. Jonathan E. Rhoads (Philadelphia, Pennsylvania): Some years after Dr. Dragstedt's study of lipocaic, I became involved in a canine study of the changes in the liver following pancreatectomy, and their prevention by giving the dogs an acid alcohol extract of pancreas developed by the Sharp & Dohme group. Related studies by the late Paul Gyorgy and associates showed that enzymes in the extract were activated in the small bowel, so that it freed methionine from food protein, thus permitting the body to synthesize choline, which is needed to prevent fatty livers.

In the belief that the short transit times after jejunoileal bypass might prevent adequate methionine release and absorption, I have given the patients 3–6 g of methionine per day and have so far not observed any hepatic complications. The material is quite inexpensive and easy to take. It needs further experimentation, but I think it may be a preventive.

Dr. Mark M. Ravitch (Closing discussion): Dr. Brolin and I are grateful for the attention our effort has received, and I assume that it is because of the intrinsic interest of the subject, rather than the size of our experience or the message which we carry.

This story began in a room like this before this Association some

20 years ago, with a paper of Dr. Arnold Kremen demonstrating that in dogs controlled malabsorption could produce weight loss and was compatible with long survival periods. At that meeting, an increasingly smaller number of you will remember that Dr. Phillip Sandblom rose to say "Yes, there is a doctor in Sweden who had done just exactly this on a patient to lose weight," and Dr. Arnold Kremen got up and said: "I was hoping nobody would mention that, but as long as it has been mentioned we've done one too," and this thing has mushroomed ever since.

We are all grateful for the pioneer studies and the long efforts of Dr. Payne and for the enormously detailed and careful scientific and methodologic studies of Dr. Scott and Drs. Buckwald and Varco. Those studies were what persuaded us, somewhat reluctantly, that we ought to undertake this problem for what has been correctly described as an otherwise unsolvable problem.

I think it is perfectly fair, though I hate to say it, and I don't believe it is necessary to repeat to this audience, as cerebral as we think we are, that, basically surgery—certainly operative surgery—is the application of mechanical principles to disease. We can accept it as axiomatic that any disease which is basically not mechanical in origin will ultimately not be treated mechanically.

Some of our most brilliant successes for a time in the history of surgery have been with mechanical procedures for nonmechanical problems, but I do not believe, in the end, vagotomy, gastrectomy, antrectomy, or any of those things, for example, are going to be the right answer to the ulcer problem. The physiologic answer ought to be; it is that the physiologists are not smart enough to arrive at that.

I must say I appreciate any support I can get anywhere, and I appreciate Dr. Wright's support since we have been enormously impressed by his work on absorption and malabsorption. My aim is to drive home "a nail in this coffin," and our abstract ends with a question. The question is: Is the game worth the candle?

For me, right now, I find that I am not able to schedule patients for a jejunoileal shunt, and it may be that I cannot face their problems as well as they can face them.

May I comment on Dr. Pace's nice paper with just one slide? We created some gastric bypasses in dogs 15 years ago (slide) and, in essence, closed off the stomach and did a gastroenterostomy around it. We found that precisely because the staples are not necrotizing instruments and the pressure is not destructive, the mucosa stays intact. It does not heal mucosa to mucosa in the undivided visius, some of the staples tear out.

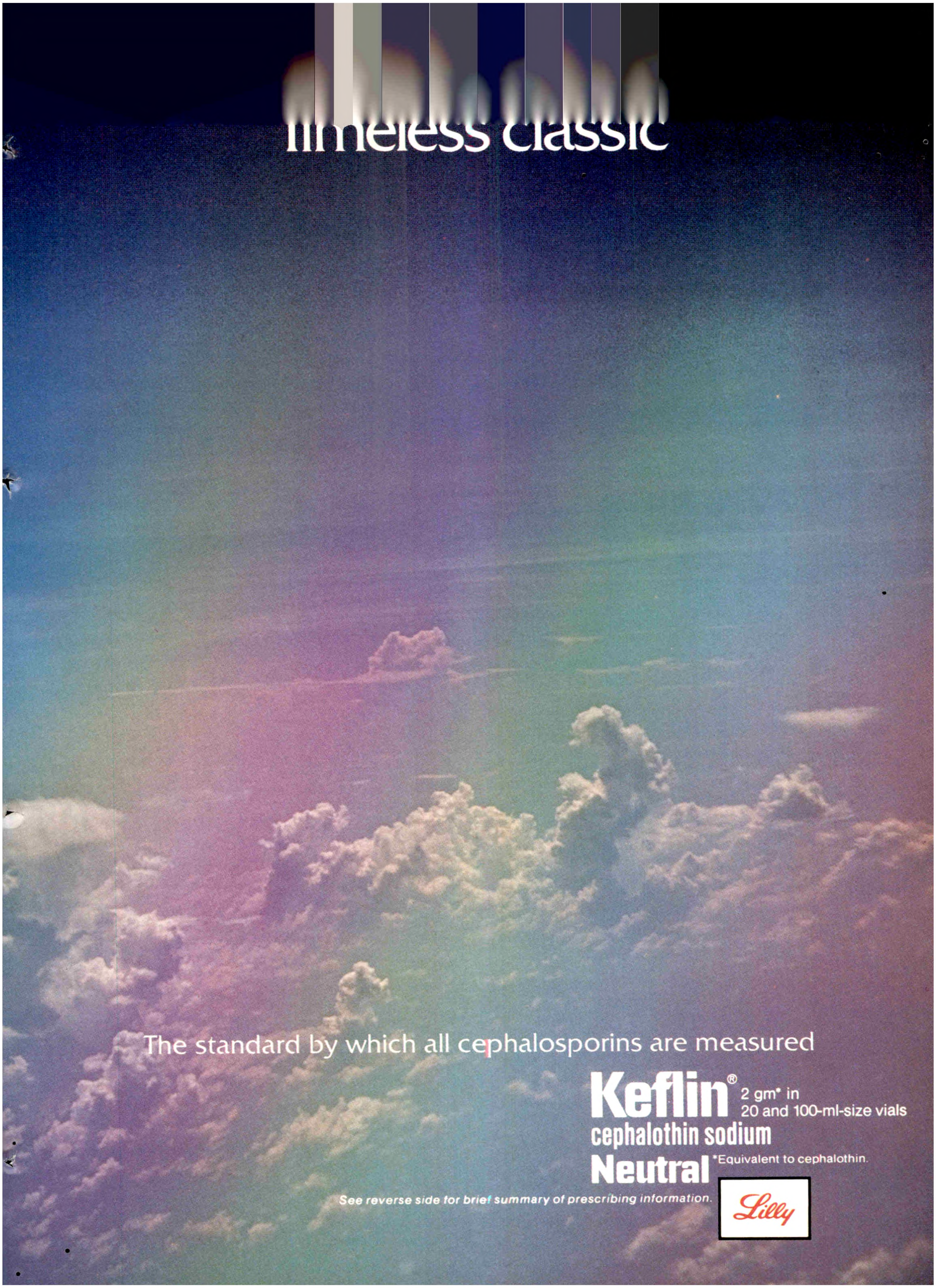
What the long-term balance will be I don't know. It is perfectly possible that enough of the staples will stay behind to maintain the reduced weight after it has been achieved. This is an interesting attempt, and somthing needs to be done for these people.

Dr. Larry C. Carey (Closing discussion): Morbid obesity presently holds a position similar to that of alcohol 20 years ago. A perception that the problem is simply a matter of character weakness is improper. Morbid obesity, like alcoholism, is a disease which leads to other diseases.

The surgical treatment of morbid obesity, much like the surgical treatment of the complications of alcoholism, is a treatment of symptoms, and not the disease. We don't understand the disease, and it ultimately will not have a surgical solution, but until we understand it better, we have, I believe, a responsible role to play in the treatment of the symptoms.

Jejunoileal bypass is the standard against which all other surgical procedures for this symptom must be compared. Now, I have, in common with Dr. Payne, a lack of experience. He has done no gastric bypasses, and I have done no jejunoileal bypasses, so we share that vacancy in experience. I suspect I will not do any jejunoileal bypasses because of the ravages of the problem that I have been witness to in following the patients that have been done by others.

Gastric partitioning will very likely not provide the ultimate solution, but it seems to be a logical step in the evolution of the surgical treatment for this disease.



Keflin® 2 gm* in
20 and 100-ml-size vials
cephalothin sodium
Neutral *Equivalent to cephalothin.

See reverse side for brief summary of prescribing information.

Lilly

Keflin®
cephalothin sodium
Neutral

Brief Summary.
Consult the package literature for prescribing information.

Indications: Keflin, Neutral, for Injection, is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below.

Respiratory tract infections caused by *Streptococcus pneumoniae,* staphylococci (penicillinase and non-penicillinase-producing), group A beta-hemolytic streptococci, *Klebsiella,* and *Haemophilus influenzae*

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and non-penicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli, Proteus mirabilis,* and *Klebsiella*

Genitourinary tract infections caused by *E. coli, P. mirabilis,* and *Klebsiella*

Septicemia, including endocarditis, caused by *S. pneumoniae,* staphylococci (penicillinase and non-penicillinase-producing), group A beta-hemolytic streptococci, *S. viridans, E. coli, P. mirabilis,* and *Klebsiella*

Gastrointestinal infections caused by *Salmonella* and *Shigella* species

Meningitis caused by *S. pneumoniae,* group A beta-hemolytic streptococci, and staphylococci (penicillinase and non-penicillinase-producing)

NOTE: Inasmuch as only low levels of Keflin are found in the cerebrospinal fluid, the drug is not reliable in the treatment of meningitis and cannot be recommended for that purpose. Keflin has, however, proved to be effective in a number of cases of meningitis and may be considered for unusual circumstances in which other, more reliably effective antibiotics cannot be used.

Bone and joint infections caused by staphylococci (penicillinase and non-penicillinase-producing)

NOTE: If the susceptibility tests show that the causative organism is resistant to Keflin, other appropriate antibiotic therapy should be instituted.

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy—Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported. [100678]

Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

801025

SECOND EDITION

■

Illustrated Preoperative and Postoperative Care

■

By Philip Thorek, M.D., F.A.C.S., F.I.C.S
Illustrated by Carl Linden

Relying on the use of original illustrations coupled with succinct, on-target text, this second edition of *Illustrated Preoperative and Postoperative Care* is a masterful exposition of Dr. Thorek's rich personal experience.

Practicality is the theme as Dr. Thorek covers evaluation of the surgical patient, the immediate post-op period, the recovery room, use of fluid and electrolytes, chemotherapy, and surgical complications. The chapter on surgical pharmacology, new to this edition, includes the concepts of alpha and beta stimulators and blockers as they pertain to the therapeutic value of various drugs.

The beautiful illustrations support the text admirably, and in many cases are fully explanatory in themselves.

"*. . . a useful reference source for neophyte or experienced surgeon alike.*"—Military Medicine

"*. . . invaluable to any student, surgeon, resident, intern or clerk, who ever intends to do surgery of any type.*"—International Surgery.

147 Pages • 79 Illus. • 2nd Edition, 1973 • $12.00

Lippincott

J. B. Lippincott Company
East Washington Square • Phila., Pa. 19105

Please send me:
☐ ILLUSTRATED PREOPERATIVE AND POSTOPERATIVE CARE $12.00

Name ______________________________
Address ______________________________
City ______________ State ____________ Zip ____________

☐ Payment enclosed Save postage & handling
☐ Charge and bill me Plus postage & handling

Also available at your medical bookstore

AS 9/79

Cook County Graduate School of Medicine

announces

ADVANCED PERIPHERAL VASCULAR SURGERY

October 15-19, 1979

A.M.A. Category I Credit: 32 Hours

Write or call for information and registration.

Registrar
707 South Wood Street
Chicago, Illinois 60612
(312) 733-2800

THE DEPARTMENT OF SURGERY
and
THE PAGE AND WILLIAM BLACK
POST-GRADUATE SCHOOL OF MEDICINE
of the
MOUNT SINAI SCHOOL OF MEDICINE (CUNY)

Announce a Postgraduate Course

THE USE OF THE CO_2 LASER IN SURGERY

Under the Direction of
EUGENE W. FRIEDMAN, M.D.
AND GUEST FACULTY

November 16, 1979

Friday—9:00 AM to 5:00 PM—1 Session

This course will be an intensive one day program consisting of lectures by eminent workers in the field. Basic physics and the workings of the various lasers will be discussed as well as the application of the laser in general surgery and its various subspecialties.

A working session with the CO_2 laser will be available where the course participants will actively use the machine.

An attempt will be made to have demonstration models of the various machines in use.

FEE: $125. (including lunch). This course will be given at the Mount Sanai Medical Center, New York City, New York

APPLY TO: Director, The Page and William Black Post-Graduate School of Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, New York 10029. Tel.: (212) 650-6737.

JOINT MEETING

SOCIEDAD ESPAÑOLA DE CIRUGIA ORAL Y MAXILOFACIAL
AMERICAN SOCIETY OF MAXILLOFACIAL SURGEONS

OFFICIAL THEME:
"RECONSTRUCTIVE CRANIO-MAXILOFACIAL SURGERY"

PROGRAMME:
1st day—Opening by the Secretary
2nd day—Instructional Courses
3rd day—First Official Theme: Craniofacial Surgery
4th day—Second Official Theme: Reconstructive Bone Surgery
5th day—Official Theme: Reconstructive Surgery of the Soft Tissues

Palma de Mallorca 1—6 June, 1980

For further Information:
Dr. E. Escutia (Secretary)
Muntaner 479—BARCELONA, 21 (Spain)

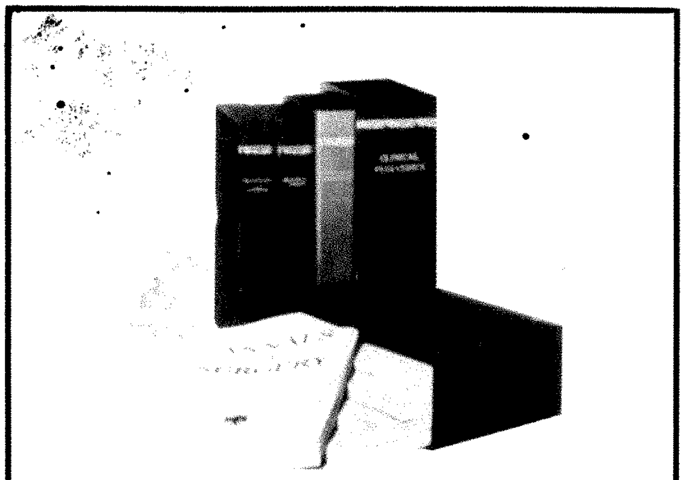
PHYSICIANS

Immediate opening for physicians who are board qualified, preferably certified, in general surgery, otolaryngology and urology at the **U. S. Public Health Service Hospital,** Norfolk, VA. Salary range dependent on qualifications. Federal benefits and malpractice coverage.

Send Curriculum Vitae to:

Director
USPHS Hospital
6500 Hampton Blvd.
Norfolk, VA 23508

Equal Opportunity Employer



PRESERVE and PROTECT YOUR COPIES OF ANNALS of SURGERY

Now, your journals can become a handsome addition to your professional library.

These file boxes are designed and custom-made to keep your copies orderly, readily accessible and clean.

Durable book-binder's board covered with scuff-resistant, washable Leathertex. Lettering embossed in 23-Karat gold leaf.

Jesse Jones Box Corp. (since 1843)
Dep't. JBLA—Phila., Pa. 19141

Gentlemen: Kindly send me:

Reasonably priced, too. Only $4.95 ea. ☐

3 for $14.00 ☐ 6 for $24.00 ☐

Add $1.00 postage per file for orders outside the U.S.

☐ Check enclosed (Make check payable to: Jesse Jones Box Corp., Box 5120, Phila., Pa. 19141)

Name ____________________

Address ____________________

City/State/Zip ____________________

Shipped postpaid U.S. only. Satisfaction unconditionally guaranteed or your money back.

PERCOCET®-5 Tablets Ⓒ II

Brief Summary of Prescribing Information

DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS

DEA Order Form Required.

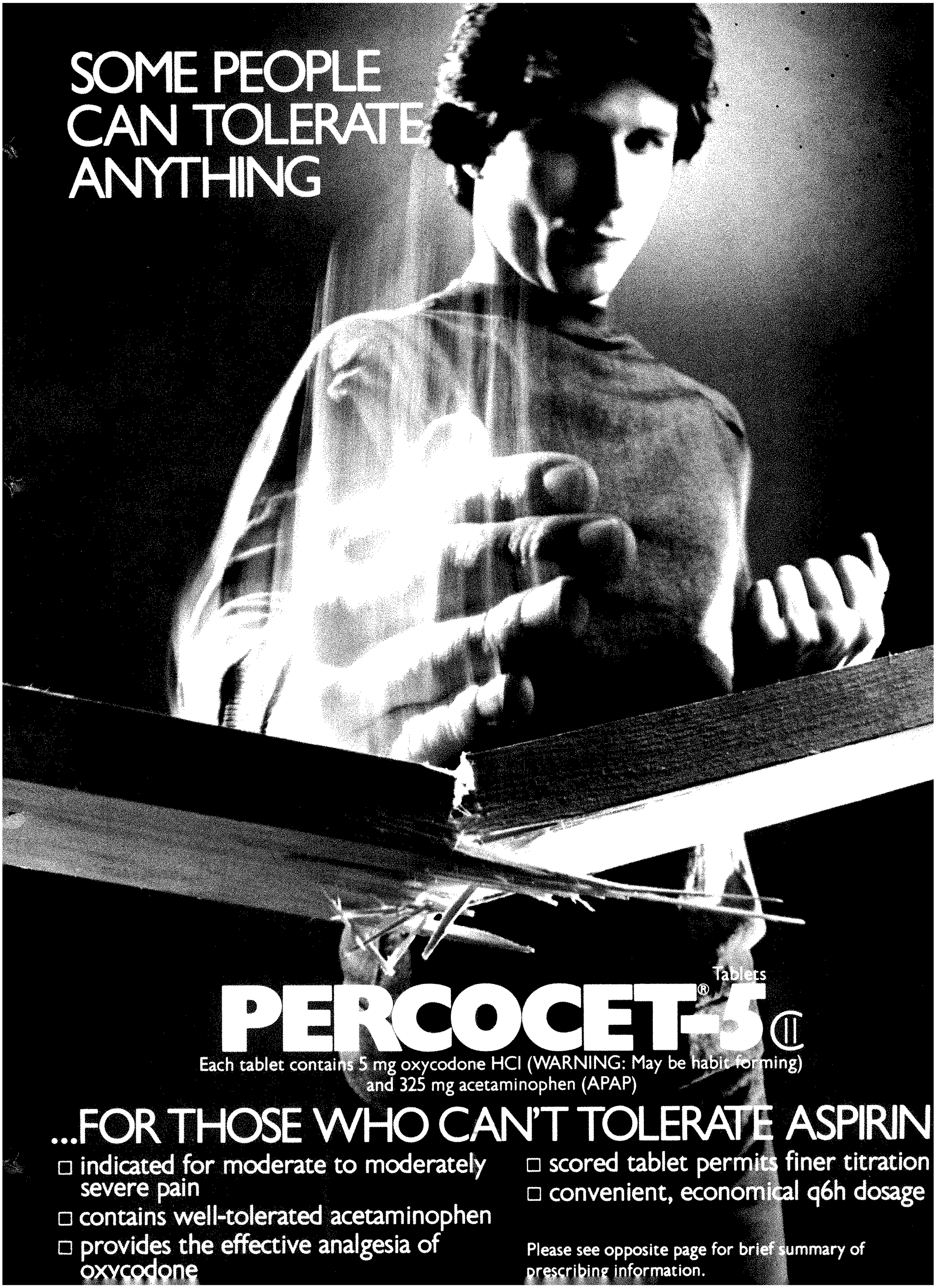
PERCOCET® is a U.S. registered trademark of Endo Inc.

Endo Inc.

Manati, Puerto Rico 00701
Subsidiary of Endo Laboratories, Inc.
Subsidiary of the DuPont Company

DUPONT

EDO-629E379



SOME PEOPLE CAN TOLERATE ANYTHING

PERCOCET®-5 Tablets Ⓒ II

Each tablet contains 5 mg oxycodone HCl (WARNING: May be habit forming) and 325 mg acetaminophen (APAP)

...FOR THOSE WHO CAN'T TOLERATE ASPIRIN

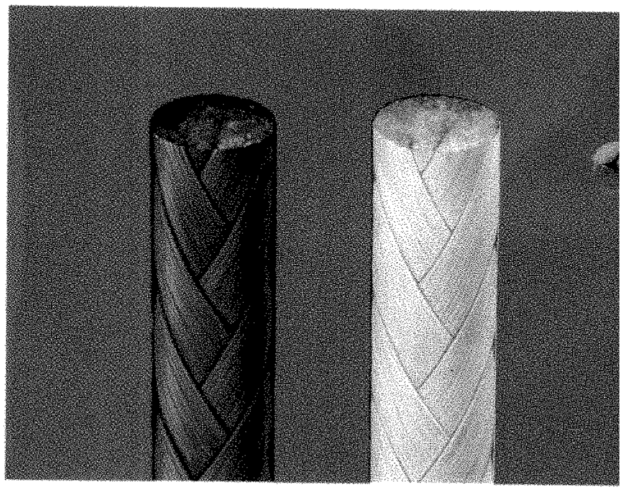
☐ indicated for moderate to moderately severe pain
☐ contains well-tolerated acetaminophen
☐ provides the effective analgesia of oxycodone
☐ scored tablet permits finer titration
☐ convenient, economical q6h dosage

Please see opposite page for brief summary of prescribing information.

ETHICON DOES IT AGAIN
VICRYL*
(Polyglactin 910) suture

Improved braided construction results in:

Superior smoothness
Better knot security
Improved handling characteristics
—In addition to the other benefits VICRYL suture is known for. Available dyed and undyed on a wide variety of needles.



Available braided, dyed and undyed.

ETHICON
the closing word

Revised 6 77

VICRYL*
(Polyglactin 910) suture

COMPLETE PRODUCT INFORMATION

VICRYL* (Polyglactin 910)
Synthetic Absorbable Suture

DESCRIPTION VICRYL (polyglactin 910) synthetic absorbable suture is prepared from a copolymer of glycolide and lactide. These substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$.

VICRYL sutures are sterile, inert, nonantigenic, nonpyrogenic, and elicit only a mild tissue reaction during absorption. The braided and monofilament sutures are colored violet to enhance visibility in tissue. The braided suture is also available undyed (natural).

ACTIONS Two important characteristics describe the *in vivo* behavior of absorbable sutures: first, tensile strength retention, and second, the absorption rate (loss of mass).

Subcutaneous tissue implantation studies of VICRYL suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of VICRYL suture is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

INDICATIONS VICRYL synthetic absorbable suture is intended for use as an absorbable suture or ligature.

CONTRAINDICATIONS This suture, being absorbable, should not be used where extended approximation of tissues under stress is required.

WARNINGS The safety and effectiveness of VICRYL (polyglactin 910) suture in neural tissue, and in cardiovascular surgery have not been established.

Under certain circumstances, notably orthopedic procedures, immobilization by external support may be employed at the discretion of the surgeon.

Do not resterilize.

PRECAUTIONS VICRYL suture knots must be properly placed to be secure. Place the first throw in precise position for the final knot, using a double loop; tie the second throw square, using horizontal tension; additional throws are advisable.

Skin and conjunctival sutures remaining in place longer than 7 days may cause localized irritation and should be removed as indicated.

Acceptable surgical practice must be followed with respect to drainage and closure of infected wounds.

ADVERSE REACTIONS Reactions reported in clinical trials which may have been suture related have been minimal. These include skin redness and induration, rare instances of hemorrhage, anastomotic leakage, wound separation in the eye, and abscesses.

DOSAGE AND ADMINISTRATION Use as required per operation.

HOW SUPPLIED VICRYL sutures are available sterile, as braided dyed (violet) and undyed (natural) strands in sizes 3 to 8-0, in a variety of lengths, with and without needles, and on LIGAPAK* ligating reels. VICRYL sutures monofilament, dyed (violet) are available in sizes 9-0 and 10-0, in a variety of lengths with needles.

Also available in sizes 1 to 4-0 attached to
CONTROL RELEASE* needles

*Trademark

ETHICON

Quick Reference To
Surgical Emergencies

■

Edited by Gerald W. Shaftan, M.D.
and Bernard Gardner, M.D.

This handy manual, packed with clinical data in easy-to-use outline form, is designed for instant use in helping you evaluate the surgical emergency, make the diagnosis and carry out the indicated treatment.

Divided into two broad categories of traumatic and non-traumatic surgical emergencies the book systematically covers: Techniques of evaluating the patient and applying diagnostic criteria . . . Radiologic procedures that are necessary . . . Anesthesia considerations . . . Fluid and electrolyte replacement.

The patient evaluating techniques, diagnostic steps and surgical treatment are presented step-by-step with each individual entry numbered for simplicity.

Subject matter includes emergencies occurring in the areas of general, orthopaedic, neurologic, ophthalmic, thoracic, plastic, urologic, head and neck, and pediatric surgery.

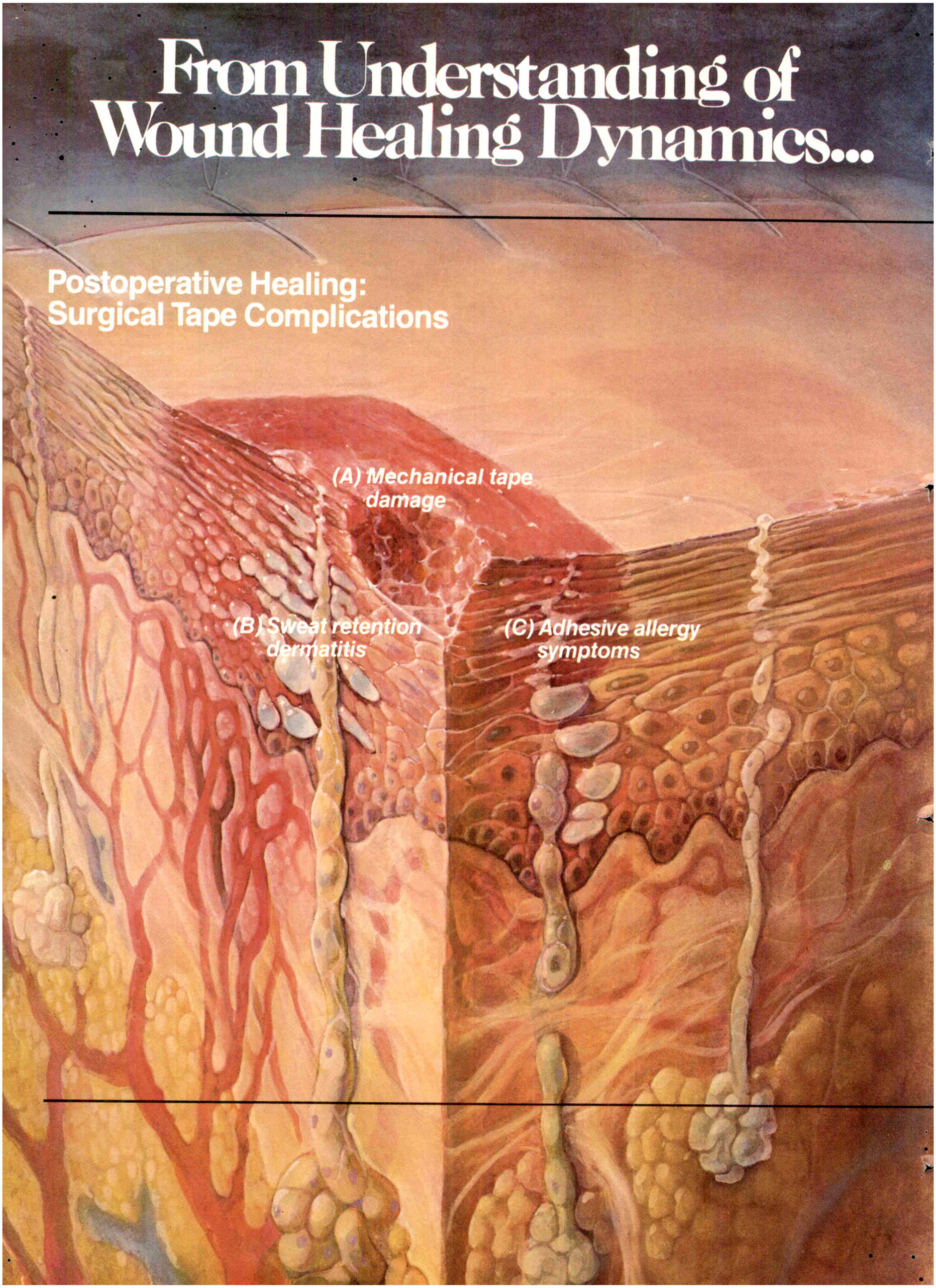
All who are involved in surgical emergency treatment will appreciate this easy-to-use, time-saving manual.

664 Pages • 50 Illustrations • 1974
Flexible Binding • $23.75

Lippincott
J. B. Lippincott Company
East Washington Square • Phila., Pa. 19105

Please send me:
☐ QUICK REFERENCE TO
SURGICAL EMERGENCIES $23.75
Name __________
Address __________
City ______ State ______ Zip ____
☐ Payment enclosed (Save postage & handling) ☐ Charge and bill me (Plus postage & handling)
Also available at your medical bookstore.
AS 9/79

From Understanding of Wound Healing Dynamics...



Postoperative Healing: Surgical Tape Complications

(A) Mechanical tape damage
(B) Sweat retention dermatitis
(C) Adhesive allergy symptoms

Come Better Products for Wound Management

Tape is a fundamental part of most wound dressings, but use of an inappropriate tape can cause complications which interfere with the healing process. This artist's interpretation of a wound in the inflammatory/fibroblastic healing stage shows the results of improper tape selection (such as misuse of non-porous or rubber base mass tape).

The most common complication (A) is the effect of occlusion. Tapes that obstruct skin surface interrupt the natural process of moisture release. Trapped moisture causes tissue to become water-logged and weakened; creates a potential breeding ground for microflora. In this weakened condition, tissue is easily damaged when tape is removed – and subject to further damage with each dressing change. Occluded sweat ducts may also produce a sweat retention rash (B).

Adhesive allergy (C) is seen less frequently, but has just as serious a potential for delaying the healing process. In a typical allergic reaction, white blood cells infiltrate the area below the tape. The area becomes inflamed and subsequently dermatitis may occur.

Consider the relationship of tape to skin and dressing

What kind of tape will hold a dressing securely, allow the skin to function normally – and come off easily without trauma, too? The only way to answer these questions is to study the character of dressings, the nature of skin. This is what we do at Johnson & Johnson. The result is a collection of tapes that meet *skin needs* as well as *clinical needs*. Excellent examples are DERMILITE II® Paper Tape and DERMICEL® CLOTH Tape. Both are hypo-allergenic, nonirritating and "breathably" porous.

Skin compatible tapes with versatility and strength

DERMILITE II Hypo-allergenic Paper Tape offers wide utility and *outperforms the leading paper tape in important ways:* It has superior adhesion and is twice as strong . . . offers greater dressing security and requires less tape. It's also gentle to skin, highly conformable and easy to remove. DERMICEL Hypo-Allergenic Cloth Tape provides the strength of a rayon backing to hold heavy multi-layer dressings. It gives you convenience with a bi-directional tear that delivers the length and width needed (without scissors). These tapes are products of understanding.

Only part of the total Wound Management System

Products such as DERMILITE II Paper Tape and DERMICEL Cloth Tape reflect the commitment of Johnson & Johnson to help improve the quality of patient care. Reinforcing our effort is the *Postoperative Wound Management* program. It's all part of the system of products, services and educational aids your Johnson & Johnson representative has to help fulfill your professional needs.

Johnson & Johnson
PRODUCTS INC.
The Leader in Wound Management

© Johnson & Johnson 1979

SURGICAL ENDOCRINOLOGY
Clinical Syndromes

●

Edited by
STANLEY R. FRIESEN, M.D., Ph.D.(Surg.)
with 28 contributors

Here is up-to-the-minute, useable information on the known endocrine syndromes requiring the attention of surgeons and other physicians. The book encompasses all the surgically significant endocrinopathies, both common and rare, all ages of patients, from the newborn to the elderly, and all accepted techniques of clinical and laboratory diagnosis, as well as surgical and conservative management.

The relevant basic sciences are integrated with current diagnostic and therapeutic techniques. Each of the contributors is a leading authority writing on his own area of special interest.

Among the unique features of this text you'll find an illuminating commentary on each chapter by Dr. Friesen . . . step-by-step diagnostic flowcharts . . . a central table of the humoral and biological actions of 20 important endocrine syndromes . . . mnemonic names for the syndromes . . . diagrammatic illustrations depicting the pathophysiology of each syndrome as a composite of clinical findings.

The volume presents a wealth of extraordinarily current developments, featuring information on such innovative concepts and practices as the APUD series of endocrine cells—their origin, identification, and clinical applications, and the future surgical management of endocrinopathies via transposition and transplantation of endocrine tissues.

430 Pages / 110 Illustrations / 1978 / $29.00

Lippincott

J. B. LIPPINCOTT COMPANY
East Washington Square ● Phila., Pa. 19105
In Canada: J. B. Lippincott Company of Canada Ltd.
75 Horner Avenue, Toronto, Ontario M8Z 4X7

Please send me:
Friesen: SURGICAL ENDOCRINOLOGY $29.00
Name ______________________
Address ______________________
City ______________ State _____ Zip _____
☐ Payment enclosed (Save postage and handling)
☐ Charge and bill me (Plus postage and handling)
Also available at your medical bookstore AS 9/79

KANTREX® CAPSULES
KANAMYCIN SULFATE
NOT FOR SYSTEMIC USE

3506DIRO-08 January 1978

DESCRIPTION
Kanamycin sulfate is a water soluble aminoglycoside antibiotic derived from **Streptomyces kanamyceticus.** It is supplied in oral formulation for topical effect within the gastrointestinal tract, because it is absorbed only very slightly when administered orally, and is excreted unchanged in the feces.

ACTIONS
Kanamycin is poorly absorbed from the normal gastrointestinal tract. The small absorbed fraction is rapidly excreted with normal kidney function. The unabsorbed portion of the drug is eliminated unchanged in the feces.

Most intestinal bacteria are eliminated rapidly following oral administration of kanamycin, with bacterial suppression persisting for 48 to 72 hours.

INDICATIONS
Suppression of intestinal bacteria.—Kanamycin is indicated when suppression of the normal bacterial flora of the bowel is desirable for short term adjunctive therapy.

Hepatic Coma.—Prolonged administration has been shown to be effective adjunctive therapy in **Hepatic Coma** by reduction of the ammonia-forming bacteria in the intestinal tract. The subsequent reduction in blood ammonia has resulted in neurologic improvement.

CONTRAINDICATIONS
This drug is contraindicated in the presence of intestinal obstruction and in individuals with a history of hypersensitivity to the drug.

WARNINGS
Although negligible amounts of kanamycin are absorbed through intact intestinal mucosa (approximately 1 percent), the possibility of increased absorption from ulcerated or denuded areas should be considered. If renal insufficiency develops during treatment, the dosage should be reduced or the antibiotic discontinued. Urine and blood examinations and audiometric tests should be given prior to and during extended therapy in individuals with hepatic and/or renal disease.

USAGE IN PREGNANCY
Safety for use in pregnancy has not been established.

PRECAUTIONS
Caution should be taken in concurrent use of other ototoxic and/or nephrotoxic antimicrobial drugs while kanamycin is administered orally. These include streptomycin, neomycin, polymyxin B, colistin, viomycin, gentamicin, and cephaloridine.

The concurrent use of potent diuretics (e.g., ethacrynic acid, furosemide, and mannitol, particularly when the diuretics are given intravenously) should be avoided. They may cause cumulative adverse effects of the kanamycin on the kidney and auditory nerve.

Prolonged use of oral kanamycin may result in overgrowth of nonsusceptible organisms, particularly fungi. If this occurs, appropriate therapy should be instituted.

ADVERSE REACTIONS
The most common adverse reactions to oral kanamycin are nausea, vomiting, and diarrhea. The "Malabsorption Syndrome" characterized by increased fecal fat, decreased serum carotene, and fall in xylose absorption has been reported with prolonged therapy. Nephrotoxicity and ototoxicity have been reported following prolonged and high dosage therapy in hepatic coma.

DOSAGE AND ADMINISTRATION FOR ORAL USE ONLY
Suppression of Intestinal Bacteria:
1. As an adjunct in therapy of Hepatic Coma for extended therapy: 8 to 12 Gm per day in divided doses.
2. As an adjunct to mechanical cleansing of the large bowel in short term therapy: 1 Gm (2 capsules) every hour for 4 hours followed by 1 Gm (2 capsules) every 6 hours for 36 to 72 hours.

Duration of therapy within this range depends on the condition of the patient, the type and amount of concurrent mechanical cleansing (catharsis and enemas), and the customary medical routine.

SUPPLY
KANTREX (kanamycin sulfate) Capsules. Kanamycin sulfate equivalent to 500 mg kanamycin per capsule.
NDC 0015-3506—500 mg

For information on package sizes available, refer to the current price schedule.

REFERENCES
1. Cohn I Jr: Test your knowledge of intestinal antisepsis, **Drug Ther** (Hosp Ed) 3:1, (Jan) 1978.
2. Rubbo SD, **et al.**: Role of preoperative chemoprophylaxis in bowel surgery. **Antimicrob Agents Chemother** 649-658, 1965.
3. LeVeen Harry H, **et al.**: **Am Journ Surg** 131, (Jan) 1976.
4. Cohn I Jr: Controlling infection in colon surgery, **Drug Ther** (Hosp Ed) 3:1, (Jan) 1978.
5. Cohn I Jr: Controlling infection in colon surgery, **Drug Ther** (Hosp Ed) 3:1, (Jan) 1978.
6. Cohn I Jr: **Surg Gynecol Obstet** 130:1006, (Jun) 1970.

BRISTOL®
©1979 BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, N.Y. 13201

When did you last use a single aminoglycoside for intestinal antisepsis... with confidence?

Among the several aminoglycosides that are typically employed for pre-op bowel sterilization, Kantrex® (kanamycin sulfate) Capsules have been recognized as "the only antibiotic that can reliably be used alone for intestinal antisepsis."[1] Recent investigations have established that Kantrex Capsules are equal in efficacy with any of the various neomycin combinations—and superior with respect to safety and minimal absorption.

"While the coliform flora was suppressed by neomycin, in approximately 70% of treated cases, the frequency of nausea, vomiting, and diarrhea was disturbingly high. Accordingly, we cannot recommend this regimen. On the other hand, the kanamycin regimen was equally efficient in suppressing the bowel flora and was not associated with any toxic side effects."[2]

"Kanamycin was chosen...because it is safer than neomycin and has a broader spectrum."[3]

"Studies with this agent have shown that its control of the bacterial flora is comparable to that of any of the combinations with neomycin."[4]

"Extensive experience has shown it to be a highly satisfactory agent—well tolerated by patients and free of some of the side effects that neomycin is prone to produce."[5]

"...it is almost quantitatively excreted in the stool and blood levels are too low to measure after oral administration."[6]

Kantrex®

KANAMYCIN SULFATE

a known quantity

BRISTOL®

©1979 BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, N.Y. 13201

Develop a Positive from a Negative.

Trauma, sepsis, injury, and disease are all catabolic processes that can deplete the body's nitrogen reserves. Aggressive nutritional support should be provided to restore a positive nitrogen balance.

Nitrogen Balance

Deca-Durabolin is a powerful anabolic steroid which promotes tissue-building processes and reverses catabolism. Used as an adjunct to other modes of nutritional therapy, Deca-Durabolin may help to develop a positive nitrogen balance. Its high anabolic/androgenic ratio allows the employment of doses that provide significant anabolic effects with reduced risk of androgenic effects.

Deca-Durabolin®

nandrolone decanoate injection, NF

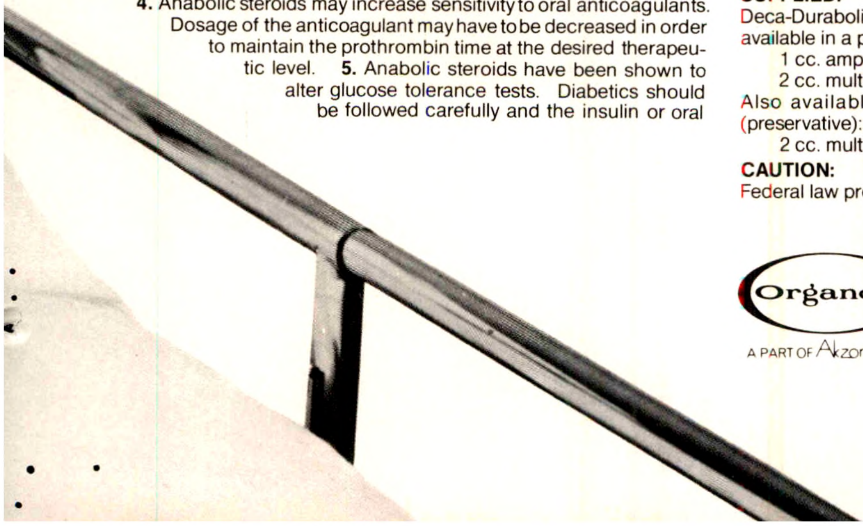
BRIEF SUMMARY: Please consult full product information in the package insert before prescribing.

> NAS/NRC review panels have classified Deca-Durabolin possibly effective in the treatment of those conditions in which a potent tissue-building or protein-sparing action is desired (e.g. pre and post surgical care, burns).

CONTRAINDICATIONS:
1. Male patients with carcinoma of the prostate or breast. **2.** Carcinoma of the breast in some females. **3.** Pregnancy, because of masculinization of the fetus. **4.** Nephrosis or the nephrotic phase of nephritis.

WARNING: Anabolic steroids do not enhance athletic ability.

PRECAUTIONS:
1. Hypercalcemia may develop both spontaneously and as a result of hormonal therapy in women with disseminated breast carcinoma. If it develops while on this agent, the drug should be stopped. **2.** Caution is required in administering these agents to patients with cardiac, renal or hepatic disease. Edema may occur occasionally. Concomitant administration with adrenal steroids or ACTH may add to the edema. **3.** If amenorrhea or menstrual irregularities develop the drug should be discontinued until the etiology is determined. **4.** Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain the prothrombin time at the desired therapeutic level. **5.** Anabolic steroids have been shown to alter glucose tolerance tests. Diabetics should be followed carefully and the insulin or oral hypoglycemic dosage adjusted accordingly. **6.** Anabolic steroids should be used with caution in patients with benign prostatic hypertrophy. **7.** Serum cholesterol may increase during therapy. Therefore, caution is required in administering these agents to patients with a history of myocardial infarction or coronary artery disease. Serial determinations of serum cholesterol should be made and therapy adjusted accordingly.



ADVERSE REACTIONS:
1. In Males: a. Prepubertal: 1) Phallic enlargement, 2) Increased frequency of erections, b. Post-pubertal: 1) Inhibition of testicular function and oligospermia, 2) Gynecomastia. **2.** In Females: a. Hirsutism, male pattern baldness, deepening of the voice and clitoral enlargement. These changes are usually irreversible even after prompt discontinuance of therapy and are not prevented by concomitant use of estrogens, b. Menstrual irregularities, c. Masculinization of the fetus. **3.** In Both Sexes: a. Nausea, b. Increased or decreased libido, c. Acne (especially in females and prepubertal males), d. Inhibition of gonadotropin secretion, e. Bleeding in patients on concomitant anticoagulant therapy, f. Premature closure of epiphyses in children. **4.** Alterations in these clinical laboratory tests: a. The metyrapone test, b. Glucose tolerance test, c. The thyroid function tests: a decrease in the PBI, in thyroxine-binding capacity and radioactive iodine uptake, d. The electrolytes: retention of sodium, chlorides, water, potassium, phosphates and calcium, e. Liver function tests: 1) Increased serum cholesterol, 2) Suppression of clotting factors II, V, VII, and X. **5.** There have been rare reports of hepatocellular neoplasms and peliosis hepatis in association with long-term androgenic-anabolic steroid therapy.

SUPPLIED:
Deca-Durabolin (in sterile sesame oil solution for intramuscular injection) is available in a potency of 50 mg./cc. with 10% benzyl alcohol (preservative):
1 cc. ampuls, box of 4. NDC #0052-0696-14
2 cc. multiple dose vial. NDC #0052-0696-02
Also available in a potency of 100 mg./cc. with 10% benzyl alcohol (preservative):
2 cc. multiple dose vial. NDC #0052-0697-02

CAUTION:
Federal law prohibits dispensing without prescription.

Organon
A PART OF Akzona INC.

Organon Pharmaceuticals
A Division of Organon Inc.
West Orange, N.J. 07052

DALMANE® (flurazepam HCl) Ⓒ
One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients).
One 15-mg capsule *h.s.*—recommended initial dosage for elderly or debilitated patients.

Before prescribing Dalmane (flurazepam HCl), please consult complete product information, a summary of which follows:
Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.
Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

> *Usage in Pregnancy:* **Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies, or with impaired renal or hepatic function. Periodic blood counts and liver and kidney function tests are advised during repeated therapy.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase
Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients.
Elderly or debilitated patients: 15 mg **recommended** initially until response is determined.
Supplied: Capsules containing 15 mg (orange and ivory); or 30 mg (red and ivory) flurazepam HCl.

ROCHE
ROCHE PRODUCTS INC.
Manati, Puerto Rico 00701

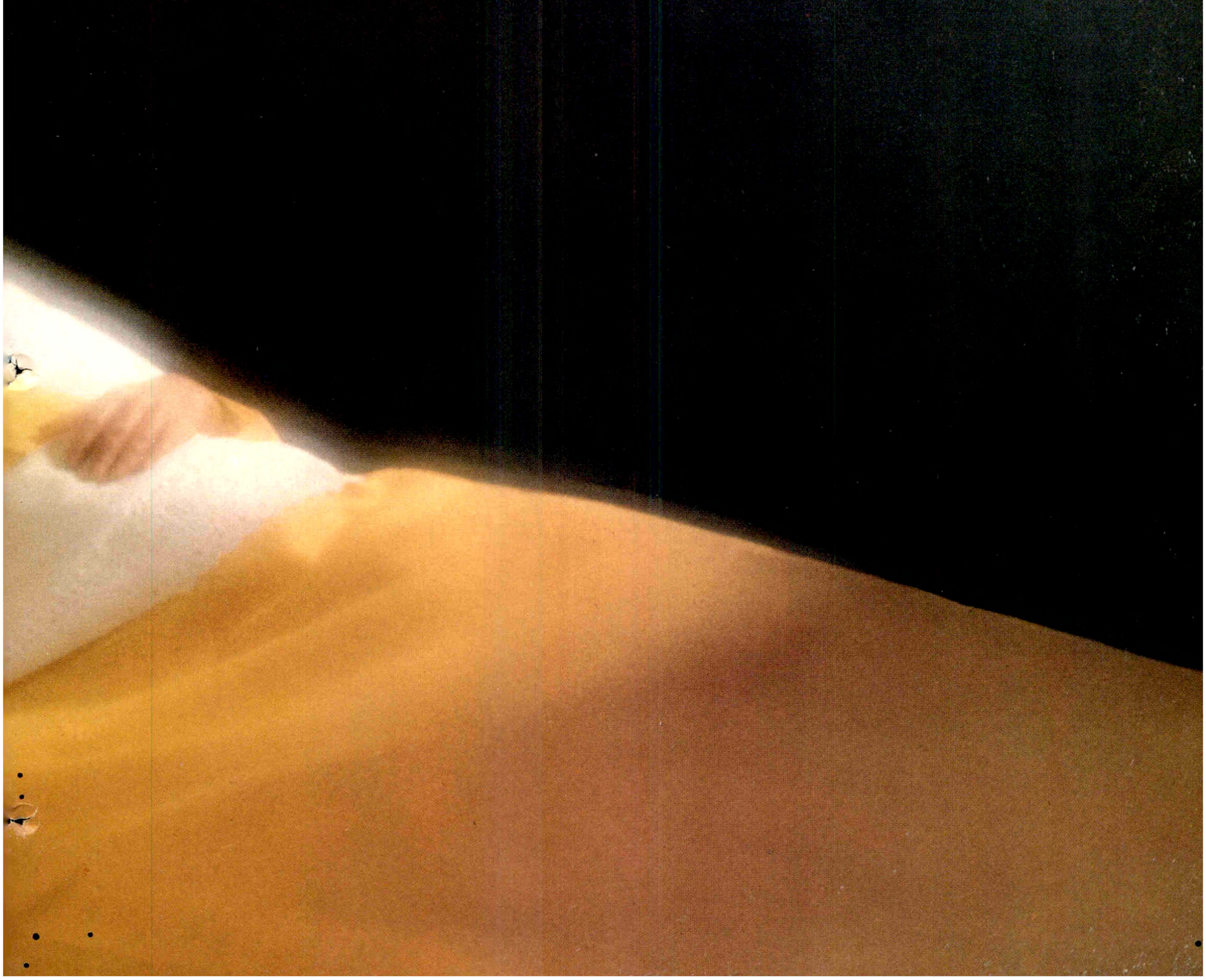
GOOD NIGHT.

Dalmane® (flurazepam HCl) provides restful sleep from the first night of administration

Of all sleep medications, none has been more thoroughly investigated and evaluated in the sleep research laboratory than Dalmane. In one study with Dalmane 30 mg *h.s.*, patients with insomnia fell asleep within 17 minutes and slept an average of 7 to 8 hours.[1]

DALMANE® CIV
flurazepam HCl/Roche
30-mg and 15-mg capsules

In another study, Dalmane was administered for 3 nights and caused significant improvement in the major parameters of sleep induction and sleep maintenance. Patients fell asleep faster, had fewer nighttime awakenings and slept longer with Dalmane.[2] And of all sleep medications, only Dalmane has been objectively proven to maintain this efficacy through at least 28 consecutive nights of administration.[2] Since insomnia is often transient and intermittent, the prolonged use of Dalmane is seldom necessary, and should only be undertaken with appropriate patient evaluations.



GOOD MORNING.

Patient usually awakens alert and refreshed

An important factor with any sleep medication is how patients feel upon awakening. Dalmane (flurazepam HCl) seldom causes morning hangover. In paired-night studies, the majority of 2010 patients reported awakening alert and refreshed after treatment with Dalmane.[1]

The usual adult dosage is 30 mg *h.s.*, but 15 mg may suffice in some patients. It is recommended that the elderly or debilitated be given 15 mg *h.s.* to help preclude oversedation, dizziness or ataxia.

References:
1. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ. **2.** Kales A, *et al: Clin Pharmacol Ther 19:* 576-583, May 1976. **3.** Moore JD, Weissman L: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ. **4.** Spiegel HE: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ. **5.** Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, pp. 641-646. **6.** Warfarin Study: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ

ROCHE

DALMANE® C IV

flurazepam HCl/Roche

30-mg and 15-mg capsules

Both *in vivo* and *in vitro* studies have established that Dalmane does not interfere with many common laboratory tests, including SGOT, glucose, uric acid, triglycerides, alkaline phosphatase and total protein.[3,4] Rare occurrences of elevations have been reported due to pharmacological effects (see Adverse Reactions section of product information).

Unlike barbiturates, which can alter the effect of coumarin anticoagulants, Dalmane may be used in patients on chronic warfarin therapy; no unacceptable fluctuation in prothrombin time has been reported.[5,6]

When a sleep medication is indicated…consider Dalmane, with an unsurpassed record of safety.

Before prescribing, please see summary of product information on first page of this advertisement.

The Natural History and Surgical Significance of Hyperlipemic Abdominal Crisis

ARNOLD MILLER, M.B.CH.B., F.R.C.S., ROBERT S. LEES, M.D., MARTHA A. MCCLUSKEY, R.N., ANDREW L. WARSHAW, M.D.

Although it is widely known that patients with severe hyperlipemia may have pancreatitis, it is not generally appreciated that such patients may have recurrent abdominal pain of variable character and intensity not due to pancreatitis. Review of 35 patients followed in our clinic for 1–11 years showed that 54% had recurrent abdominal pain, while only 29% had pancreatitis. Although mild pain occurred frequently with plasma triglycerides in the 2000–5000 mg/dl range, triglycerides over 6000 mg/dl were often associated with severe pain and physical findings which necessitated hospitalization, often led to the misdiagnosis of pancreatitis and other intra-abdominal catastrophes and resulted in multiple unnecessary diagnostic studies and operations. When recognized, the pain subsided within 48 hours upon cessation of oral intake and treatment with intravenous electrolyte solutions. Furthermore, effective treatment of the hyperlipemia prevented both the attacks of severe pain and the pancreatitis which otherwise occurred (or recurred) in a significant fraction of the patients. These data confirm the existence of hyperlipemic abdominal crisis as a distinct entity and testify to the importance of recognizing this syndrome in order to avoid the occurrence of acute pancreatitis and the performance of unnecessary and potentially harmful surgery.

THE ASSOCIATION OF HYPERLIPEMIA and pancreatitis, although described more than 100 years ago, was only recently recognized as a causal relationship.[2,9] The hyperlipemia has most often been ascribed to excessive alcohol ingestion. Fredrickson and Lees,[6] in their classification of familial hyperlipoproteinemias, described two groups of patients, Type I and Type V, who were susceptible to attacks of pancreatitis. In addition, many of these patients suffered recurrent episodes of abdominal pain of varying severity and character without the clinical manifestations of pancreatitis. The usual laboratory differentiation between these attacks of abdominal pain and acute pancreatitis based upon an elevation of the serum amylase has been found to be unreliable due to inhibition of the serum amylase activity in the presence of hyperlipemia.[19]

From the Arteriosclerosis Center, Massachusetts Institute of Technology, and the Surgical and Medical Services, Massachusetts General Hospital and Harvard Medical School, Cambridge and Boston, Massachusetts

Whether these episodes of pain are truly pancreatitis, a precursor of pancreatitis or something entirely different, the condition in patients suffering from these "hyperlipemic abdominal crises" is often unrecognized, misdiagnosed and subjected to mistreatment, including unnecessary surgery. The purpose of this paper is to draw attention to the syndrome of "hyperlipemic abdominal crisis" and to describe its natural history, treatment and prevention.

Clinical Material and Methods

Thirty-five patients with proven Type V hyperlipoproteinemia investigated and treated at the Arteriosclerosis Center, Massachusetts Institute of Technology, between the years 1969–1978 were included in this study (Table 1). The minimum period of follow-up was 1 year. The patients were referred from the Massachusetts General Hospital, from other major centers and from individual physicians. Hyperlipemia had been detected in all cases prior to referral, and in a number of patients treatment had already begun with diet and lipid-lowering agents. They were referred to our center either because of unsatisfactory control of their hyperlipemia or because of recurring episodes of abdominal pain or acute pancreatitis.

The diagnosis of acute pancreatitis in these patients, as opposed to uncomplicated hyperlipemic abdominal pain, was based mainly upon standard clinical characteristics, corroborated whenever possible by laboratory features, such as elevation of serum amylase or depression of serum calcium. Five of the 11 patients who suffered attacks of pancreatitis were evaluated and treated for at least one episode at the Massachusetts General Hospital. For attacks occurring before

---

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

Reprint requests: Robert S. Lees, M.D., Arteriosclerosis Center, Massachusetts Institute of Technology, Cambridge, Massachusetts 02142.

0003-4932/79/0900/0401 $00.90 © J. B. Lippincott Company

TABLE 1. *Clinical and Laboratory Characteristics of Patients with Type V Hyperlipoproteinemia*

						Plasma Cholesterol (mg/dl)				Plasma Triglycerides (mg/dl)					
						Pre Rx		Post Rx		Pre Rx		Post Rx			
Patient	Age at Diagnosis	Sex	Eruptive Xanthomas	Visceromegaly*	Glucose Intolerance	Lowest	Highest	Lowest	Highest	Lowest	Highest	Lowest	Highest	Symptomatic Arteriosclerosis	Height-Weight Index
No Pain															
1	42	M	+	–	–	289	577	158	280	651	2586	111	396	–	247
2	51	M	–	–	–	261	328	277	329	293	594	273	414	–	226
3	60	F	–	–	+	410	727	190	352	2420	7050	800	1665	+	305
4	63	F	–	–	–	315	540	212	241	518	1503	229	1433	–	235
5	39	M	–	+	–	286	332	298	367	1447	3234	2331	3103	–	243
6	45	M	–	–	–	250	265	170	238	465	844	64	122	–	236
7	58	M	+	–	–	320	395	151	237	2684	2684	92	670	–	294
8	40	M	–	–	–	296	359	141	311	1435	3490	255	1673	–	240
9	39	M	–	–	–	254	301	168	315	695	1377	103	1769	–	266
10	58	M	–	–	–	242	266	141	242	1230	1695	113	416	–	236
11	45	F	–	–	–	293		—	—	1487	2600	—	—	–	244
12	43	M	+	–	–	360	392	158	235	1241	2997	179	552	–	256
13	37	M	–	–	–	182	259	252		1280	2436	752		–	328
14	51	F	–	–	–	298	376	241	251	177	1480	368	1140	+	275
15	46	F	+	+	+	447	594	423		2880	4709	2703		+	384
16	65	M	–	–	–	28	319	266	232	1453	1900	473	693	+	261
Abdominal Pain															
Subgroup A — Pancreatitis at Presentation															
17	42	M	–	–	–	238	268	214	380	1278	2030	226	793	–	225
Subgroup B — Pain and Pancreatitis															
18	23	F	–	+	–	181	277	131	216	280	2300	196	1058	–	243
19	40	M	+	–	+	140	1071	71	139	596	8400	173	792	+	287
20	40	F	–	+	+	110	205	74	125	235	10000	210	1459	–	275
21	38	F	+	–	–	217		217	604	3600	10000	190	3606	–	274
22	24	F	–	–	–	170	461	149	183	210	2100	140	210	–	238
23	32	F	+	–	–	255	414	180	1420	300	7100	462	928	–	274
24	22	F	–	–	–	277	306	166	250	153	1366	115	321	–	232
25	52	M	–	–	–	300	500	185	431	4000	10000	3796	6051	–	243
26	42	F	+	+	+	495	900	289	656	5000	9000	1265	6084	+	275
27	24	F	–	–	+	159	170	157	182	500	1000	230	351	–	280
Subgroup C — Pain Only															
28	36	F	–	+	+	150	500	240		200	4000	815		–	268
29	38	F	–	–	–	277	548	195	504	940	10800	106	4815	–	204
30	65	F	–	+	+	226	354	202	346	1313	2624	88	1497	+	238
31	41	F	–	+	–	304	531	312		1077	1514	1488		–	334
32	14	M	+	+	–	206	248	164	220	1001	5000	247	1601	–	272
33	46	M	–	+	–	263	400	220	356	485	1830	134	537	+	265
34	45	F	–	–	+	97	510	143	253	1705	11000	650	3872	–	234
35	32	M	+	–	+	222	764	86	248	5240	11371	109	225	–	260

* Enlargement of liver, spleen or both.

the patients were referred to us, the diagnosis of pancreatitis by the referring physician was accepted.

The diagnostic work-up and phenotyping of the hyperlipemia in these patients included a complete history and physical examination, repeated serum lipid evaluation, lipoprotein paper electrophoresis and lipoprotein quantification performed in our laboratories by the methods described by Lees and Hatch[13] and Hatch and Lees.[10]

Once the diagnosis and typing were confirmed, the patients were managed in a standardized fashion. Initially all patients were placed on a low-fat (less than 30 gm/day) weight reduction diet. None of these patients drank alcohol to excess. All were advised to consume no more than the equivalent of 2 oz. of alcohol per day; those with pancreatitis were advised to abstain completely. Lipid-lowering drugs (Table 2) were added, depending on response. Choice of drug and dose were adjusted by individual patient response and were monitored by measurement of serum cholesterol and triglycerides. In six patients 85–90% jejunoileal bypass was performed.[17]

The statistical significance of differences between means was assessed by the Wilcoxon Rank Sum Test.[20]

Results

The 35 Type V hyperlipoproteinemic patients in this study could readily be divided into two groups according to their clinical presentation. There were 19 pa-

TABLE 2. *Lipid-lowering Agents Used*

Drug	Daily Dose
1. Clofibrate	1–2 gm
2. Nicotinic acid	0.5–4 gm
3. Oxandrolone	2.5–7.5 mg
4. Norethindrone acetate	5 mg

tients who had experienced multiple episodes of abdominal pain with or without attacks of pancreatitis and 16 patients who had never suffered any episodes of abdominal pain or pancreatitis. Table 1 summarizes the clinical features of these groups.

The mean age of patients presenting with abdominal pain or pancreatitis was approximately a decade younger than that of the pain-free group, 36 years vs. 49 years ($p < 0.01$). The sex ratio in the two groups was reversed, with females predominating about 2:1 in those suffering abdominal pain and males predominating about 2:1 in the group without pain. Both groups were equally obese, as reflected by their height-weight index[12] (Table 3). The incidence of symptomatic arteriosclerosis, similar in the two groups, was relatively low, as previously noted.[14]

Clinical features usually associated with more severe hyperlipemia, including hepatosplenomegaly, eruptive xanthomas and glucose intolerance, were not significantly more frequent in the abdominal pain group.

The highest mean pretreatment plasma triglyceride concentrations in the group presenting with abdominal pain were much higher than those in the pain-free group (5865 mg/dl vs. 2573 mg/dl [$p < 0.05$]).

There was a striking difference between these two groups in the number of contrast x-ray examinations and operations performed. An average of 2.3 contrast examinations per patient were performed in the abdominal pain group as opposed to 0.7 per patient in the pain-free group. Nine patients with abdominal pain were subjected to 22 major abdominal operations, whereas in the pain-free group only five patients each underwent a single major abdominal operation (1.2 operations per patient in the group with pain versus 0.3 per patient in the group without pain). The operative procedures are listed in Table 4.

Further analysis of the 19 patients presenting with both abdominal pain and hyperlipemia enabled them to be subdivided into two and possibly three subgroups by their clinical presentation: A) pancreatitis as the initial manifestation (Patient 17, Table 1); B) multiple episodes of abdominal pain of varying severity preceding one or more attacks of acute pancreatitis (Patients 18–27, Table 1); C) multiple episodes of abdominal pain, similar to those in subgroup B, without progression to acute pancreatitis (Patients 28–35, Table 1).

One patient in Subgroup A, a 42-year-old man, was admitted in 1973 with severe acute pancreatitis. He had no previous history of abdominal pain or recent ingestion of alcohol. The plasma triglycerides, first measured 1 week after onset of pancreatitis, were 2030 mg/dl. His hospital course was prolonged and complicated by acute respiratory failure. Following recovery he was treated with lipid-lowering agents and diet and has remained completely asymptomatic. Because the significance of this one case cannot be evaluated, he has been excluded from further comparison between Subgroups B and C.

There were minor differences in mean age of presentation between Subgroup B (34 years) and Subgroup C (39 years). Both groups showed a similar degree of obesity, and there was no difference in the incidence of hepatosplenomegaly, glucose intolerance or symptomatic arteriosclerosis (Table 1).

In Subgroup B, the interval between the onset of the first episode of abdominal pain and clinical pancreatitis ranged from one month to 15 years, with a mean of 3.5 years. However, four of the 10 patients presented

TABLE 3. *Clinical Features of Patients With and Without Abdominal Pain*

		Abdominal Pain	No Pain
No. patients		19	16
Mean age in years at diagnosis (range)		36 (14–65)	49 (37–65)
Male:female		6:13	11:5
Eruptive xanthomas		6	4
Visceromegaly (liver and/or spleen)		8	2
Glucose intolerance		7	2
Symptomatic arteriosclerosis		5	3
Height-weight index* (Mean)	Male	259	258
	Female	259	289
Highest pretreatment lipids (mean ± SD)	Plasma cholesterol	455 ± 241	395 ± 139
	Plasma triglycerides	5865 ± 3983	2573 ± 1592

* Normal index: 200–235 for males; 190–205 for females.[12]

TABLE 4. *Operations Performed on Hyperlipemic Patients With or Without Abdominal Pain*

Patient	Operation
With Pain	
18	Cholecystectomy
20	Appendectomy Cholecystectomy (cholelithiasis)
21	Cholecystectomy Exploratory laparotomy (pancreatitis) Transduodenal sphincteroplasty
22	Appendectomy Lysis of adhesions (intestinal obstruction) Exploratory laparotomy (pancreatitis)
25	Appendectomy Splenectomy (trauma) Cholecystectomy
27	Cholecystectomy Exploratory laparotomy (pancreatitis) Transduodenal sphincterotomy
29	Cholecystectomy Exploratory laparotomy
31	Exploratory laparotomy Drainage of pelvic abscess
34	Cholecystectomy Transduodenal sphincterotomy Drainage of pancreatic abscess
Without Pain	
3	Cholecystectomy (cholelithiasis)
4	Appendectomy
5	Splenectomy (trauma)
7	Appendectomy
10	Appendectomy

with clinical pancreatitis within one year, and six patients presented within two years of their first episode of abdominal pain. In Subgroup C, the mean duration of the onset of the recurrent episodes of abdominal pain prior to referral to our clinic was from 2 to 29 years, with a mean of 12.3 years.

In both groups the attacks of episodic pain were multiple. The nature of the pain varied from patient to patient and in the same patient from time to time. The severity of the attack varied from vague upper abdominal pain to that sufficient to necessitate hospitalization to exclude the more common causes of abdominal pain such as appendicitis, cholecystitis, peptic ulcer and pancreatitis. The pain sometimes mimicked hepatic or splenic infarction and was often associated with abdominal guarding and rigidity, as well as fever, leukocytosis and elevated erythrocyte sedimentation rate.

There was no significant difference in the number of x-ray contrast studies performed in Subgroups B (2.7 per patient) and C (2.3) nor in the number of operations performed per patient. Roughly half the patients of each subgroup underwent major abdominal surgery related to the abdominal pain. In the two subgroups there were five exploratory laparotomies. In three of the five pancreatitis was found. Another two patients were subjected to appendectomy, although they did not have appendicitis by histology. Two additional patients were subjected to cholecystectomy, although no disease was found. Thus, at a minimum, six operations—two laparotomies, two appendectomies and two cholecystectomies—were in retrospect found to have been performed unnecessarily. Documentation of pathology in remaining cases was not obtainable, but it remains uncertain whether the two sphincterotomies and the sphincteroplasty were really necessary in the treatment of the recurrent attacks of abdominal pain or pancreatitis.

Three patients developed complications from what appears in retrospect to have been unnecessary surgery. Of the two patients with normal appendices, one developed a postoperative pelvic abscess requiring drainage, while the other developed adhesive obstruction requiring lysis of the adhesions. A third patient was subjected to transduodenal sphincterotomy for recurrent episodes of abdominal pain and developed a postoperative pancreatic abscess which required drainage.

The highest pretreatment plasma triglycerides for Subgroups B and C are shown in Table 1. The mean for Subgroup B was 6127 mg/dl and for C was 6017 mg/dl. This difference was not statistically significant.

The highest plasma triglyceride levels were usually recorded around the time of an attack of severe abdominal pain or pancreatitis. The patients listed in Table 5 all had their plasma lipids measured during a hyperlipemic abdominal crisis. These are the only five patients for whom this information was available. Even at our institutions, admitting physicians and surgeons have not been attuned to watching for lactescent plasma or measuring plasma triglycerides in patients with abdominal pain.

Many patients, especially the group with pancreatitis, were noted to have lactescent plasma on initial presentation but did not have actual measurement of plasma lipids until the pain had begun to abate, 24

TABLE 5. *Plasma Lipid Values Documented at Admission for Hyperlipidemic Abdominal Crisis*

Patient	Cholesterol (mg/dl)	Triglycerides (mg/dl)
19	1071	8400
23	1420	7100
25	486	6790
29	548	10800
35	764	11371

TABLE 6. *Results of Treatment in Subgroup B Patients*

Patient	Diet	Drugs	Intestinal Bypass	Highest Plasma Triglycerides (mg/dl)		Occasional Mild Pain	Pan-creatitis	Duration of Follow-up (yrs)
				Pre Rx	Post Rx			
18	+	+	–	2300	1058	+	–	11
19	+	+	+	8400	792	+	–	5
20	+	+	+	10000	1459	+	–	3
21	–	+	+	10000	3606	+	–	3
22	+	–	–	2110	210	+	–	1
23	+	–	–	7100	928	–	–	1
24	+	+	–	1366	321	+	–	7
25	+	+	–	10000	6051	+	–	3
26	+	+	–	9000	6084	+	–	2
27	+	–	+	1000	351	+	–	3
Mean				6127	2086			3.9

hours or longer after treatment was initiated. Many very much milder episodes of abdominal discomfort, usually not necessitating urgent medical attention, were associated with plasma triglycerides in the range of 2000–5000 mg/dl.

Diet was the initial treatment for all patients in Groups B and C. Although the goals of the diet were weight reduction as well as low fat content, no patient in either group maintained a weight loss of 10 lbs. or more on diet alone. However, most patients were careful to maintain a low-fat diet, and, once treatment had been established, most episodes of abdominal pain were usually related by the patients to dietary indiscretions associated with high fat intake.

In Subgroup B, two of the 10 patients were treated by diet alone. Four patients were treated with lipid-lowering agents in addition to diet, and the remaining four patients were subjected to ileal bypass, three because of poor response to medical treatment and the fourth because of massive obesity and inability to lose weight by diet control (Table 6).

The plasma triglyceride response to treatment in Subgroup B is recorded in Table 6. Highest recorded plasma triglyceride concentrations fell from a mean of 5312 mg/dl to 2442 mg/dl (54%) with medical treatment alone and from 7350 mg/dl to 1552 mg/dl (73.5%) following jejunoileal bypass surgery. Three of the four ileal bypass patients remained on lipid-lowering agents postoperatively.

Of the ten patients in Subgroup B, only one patient, treated by diet alone, was free of pain one year after treatment was begun. All the others still experienced occasional mild attacks of abdominal pain, but these were clearly less frequent and less severe than prior to treatment. Moreover, during a mean follow-up period of four years (range, 1–11 years) none has subsequently developed another attack of acute pancreatitis.

The findings in Subgroup C are similar (Table 7). Two of the eight patients were treated by diet alone. Four others were treated with lipid-lowering agents and diet, and an additional two patients underwent ileal bypass surgery after having failed to respond to medical therapy.

The highest recorded plasma triglyceride concentrations for Subgroup C fell following treatment from a mean of 6017 mg/dl to 1856 mg/dl (69.2%). Comparable reductions were seen with both medical therapy and ileal bypass.

At time of follow-up of 1–11 years (mean 5.6 years) of the eight patients in Subgroup C, four were asymptomatic: one by diet alone, another with lipid-lowering agents and diet and two following ileal bypass surgery.

TABLE 7. *Results of Treatment in Subgroup C Patients*

Patient	Diet	Drugs	Intestinal Bypass	Highest Plasma Triglycerides (mg/dl)		Occasional Mild Pain	Pan-creatitis	Duration of Follow-up (yrs)
				Pre Rx	Post Rx			
28	+	–	–	4000	815	–	–	1
29	+	+	–	10800	4815	+	–	11
30	+	+	–	2624	1497	–	–	7
31	+	–	–	1514	1488	+	–	1
32	+	+	–	5000	1601	+	–	11
33	+	+	–	1830	537	+	–	6
34	+	+	+	11000	3872	–	–	3
35	+	+	+	11371	225	–	–	5
Mean				6017	1856			5.6

Discussion

Our data show that the variable clinical manifestations of Type V hyperlipoproteinemia are directly related to the patients' plasma lipid concentrations. Although some patients may be asymptomatic with the hyperlipemia discovered on routine blood examination, others present with recurrent episodes of abdominal pain of varying severity or even with acute pancreatitis. Patients with Type V hyperlipoproteinemia are thus exposed to a significant risk both from serious illness and from unwarranted, potentially harmful surgical intervention because of these hyperlipemic abdominal crises.

The prevalence of hypertriglyceridemia in subjects hospitalized for pancreatitis has been variously estimated at 12–53%.[2,5,9,18] Most of the series included a large number of alcoholic patients. Inasmuch as alcohol may be associated with both hyperlipemia and pancreatitis, perhaps independently and without a causal relationship, studies of alcoholic patients potentially lead to overestimation of the frequency with which pancreatitis occurs *as a result of hyperlipemia*. Estrogen administration (usually given in oral contraceptives or for treatment of carcinoma of the prostate) to subjects with Type V hyperlipoproteinemia has only recently been recognized as causing exacerbation of the hypertriglyceridemia and leading to pancreatitis.[7]

Approximately half the patients (54%) in our study presented with abdominal pain. Twenty-nine per cent of the entire group developed acute pancreatitis, an incidence similar to that in the study of Greenberg et al.[8] It is the plasma triglyceride concentrations rather than the plasma cholesterol concentrations that appear to be causally related to the hyperlipemic abdominal crisis. Patients presenting with severe abdominal pain or pancreatitis all had triglycerides in excess of 6000 mg/dl, while lesser attacks were associated with plasma triglycerides between 2000 mg/dl and 5000 mg/dl. In contrast, patients with other forms of familial hyperlipidemia characterized primarily by hypercholesterolemia rather than hypertriglyceridemia, such as Type II hyperlipoproteinemia, do not develop either abdominal pain or pancreatitis.[14]

It was impossible to predict on clinical grounds alone the likelihood that a given patient would have abdominal pain. The incidence of the more common clinical manifestations of Type V hyperlipoproteinemia, such as obesity, glucose intolerance, eruptive xanthomas and visceromegaly, was similar in the two groups. However, there were three notable differences between the patients with and without pain: 1) those presenting with hyperlipemic abdominal crises did so at an earlier age; 2) females predominated in the group with pain, and 3) the peak pretreatment serum triglyceride levels were significantly higher in the patients with pain. Although the plasma triglycerides were higher in the patients with pain than in those without pain, it was not possible to identify a threshold plasma triglyceride concentration above which pain inevitably occurred. The converse was not true: it was possible to specify a plasma triglyceride concentration below which pain did not occur, approximately 2000 mg/dl.

Analysis of the patients with abdominal pain showed three fairly distinctive patterns of presentation. Two of the three patient subgroups had severe signs and symptoms. One patient developed acute pancreatitis with no previous abdominal pain. Ten patients had acute pancreatitis 1 month to 15 years (mean 3.5 years) after the onset of attacks of pain. This is in marked contrast to the third group of patients, who presented with recurrent episodes of abdominal pain over a period of 2–29 years (mean 12.3 years) yet did not go on to develop acute pancreatitis. Since the pretreatment plasma triglycerides were comparable among all patients with abdominal pain, it is unclear why some patients had only hyperlipemic crisis, while others progressed to unequivocal acute pancreatitis. One might postulate that another factor in addition to hypertriglyceridemia, perhaps interacting with it, must be present to trigger pancreatitis. Alternatively, pancreatitis may be a risk in any given hyperlipemic crisis, but one of low statistical probability.

The cause of the abdominal pain of severe hyperlipemia is obscure. It is tempting to consider all such pain as representative of pancreatitis, either overt or occult. However, the case against this contention is supported by both clinical and biochemical evidence. In some patients with abdominal pain, rapid enlargement of liver and/or spleen occurs, and these organs become exquisitely tender to palpation; furthermore, palpation reproduces or exacerbates their presenting pain. In one patient in our study, an exploratory laparotomy performed during a hyperlipemic crisis revealed moderate amounts of "murky" fluid with some serosal inflammation "suggestive of peritonitis." The usual fat necrosis and swelling of the pancreas, the hallmarks of pancreatitis, were absent. Analysis of this free fluid for amylase content has, to our knowledge, never been performed. In other patients, attacks which we have designated as hyperlipemic abdominal crisis have milder clinical features than those of pancreatitis, including absence of requirement for plasma volume support and absence of the usual laboratory features of pancreatitis (hyperamylasemia, hypocalcemia and increased amylase/creatinine ratio). We recognize that this differential diagnosis of hyperlipemic abdominal crisis is potentially complicated by the fact that hypertriglyceridemia may obscure rises in serum amylase[4,19] unless special dilutional and other methods[15,19] are applied. We have used these techniques in recent years. Elevation of serum pancreatic isoamylases is a hallmark of acute pancreatitis (Warshaw, A. L., unpublished observations). We have measured these enzymes in three of our Subgroup C patients during a hyperlipemic abdominal crisis and found that they were not elevated. At present we must still consider the pain of most hyperlipemic abdominal crises not to be due to pancreatitis.

The recent description of a patient with severe hyperlipemia and recurrent pancreatitis secondary to the congenital absence of apolipoprotein C-II, the normal cofactor for the enzyme lipoprotein lipase, has provided for the first time a specific biochemical defect in at least a small subset of patients with Type V hyperlipoproteinemia.[1] However, in most patients with this relatively common hyperlipemic syndrome, the biochemical defect remains unknown. Lipoprotein lipase is the enzyme which is responsible for the removal of lipoprotein triglycerides from plasma; complete absence of the enzyme itself results in the rare Type I hyperlipoproteinemia, which is also characterized by severe hyperlipemia and recurrent pancreatitis.[6,14]

How hypertriglyceridemia causes pancreatitis is not well established. Havel[11] has suggested that exposure of circulating triglycerides to lipase in the pancreatic capillaries could result in hydrolytic formation of free fatty acids, which cause local tissue injury, release of pancreatic enzymes and consequent autodigestion. This hypothesis has been supported by an experimental model using an isolated pancreas.[16]

Our study shows that lack of awareness of the existence of hyperlipemic abdominal pain results in significant morbidity, both from the vast numbers of unnecessary investigations undertaken and from the variety of unnecessary operative procedures performed. Plasma triglycerides during the acute episodes are invariably very high; the diagnosis of hyperlipemic abdominal crisis can often be made by gross examination of the patient's plasma, which becomes frankly creamy during attacks. If untreated, subjects prone to pancreatitis may proceed from simple reversible hyperlipemic crisis to life-threatening acute pancreatitis.

Initial treatment is simple and requires the cessation of all oral intake, while maintaining the patient's fluid and electrolyte balance with saline solutions. In patients already presenting with pancreatitis, recognition of hypertriglyceridemia may eliminate the need for exploratory laparotomy and promote more confident diagnosis and rational treatment.

Perhaps the most important reason for the recognition of this group of patients is the dramatic manner in which the clinical course may be influenced in all patients with abdominal pain by reducing the plasma triglycerides. Whether treated by diet alone, diet and lipid-lowering agents or by ileal bypass, a significant reduction in lipid values was achieved in almost all cases. Once adequate treatment had been instituted, no patient developed further attacks of pancreatitis. In all patients, the attacks of hyperlipemic abdominal pain became less frequent and much less severe, although those attacks did not disappear completely in the majority. Most patients learned to recognize their "pain" while it was only mild discomfort and by modifying their diet prevented their previously full-blown attacks.

Despite the knowledge that a patient is hyperlipemic and prone to hyperlipemic crises, each episode of abdominal pain should be evaluated afresh on its characteristics. Hyperlipemic patients are susceptible to the same spectrum of illness as the general population. During follow-up, patients known to have suffered previously from hyperlipemic crises or pancreatitis have presented with abdominal pain from gastric ulcer, duodenal ulcer, ureteral colic, perforated diverticulitis and intestinal obstruction from carcinoma of the colon.

References

1. Breckenridge, C. W., Little, A., Steiner G. et al.: Hypertriglyceridemia Associated with Deficiency of Apolipoprotein C-II. N. Engl. J. Med., 298:1265, 1978.
2. Cameron, J. L., Capuzzi, D. M., Zuidema, G. D. and Margolis, S.: Acute Pancreatitis with Hyperlipidemia. The Incidence of Lipid Abnormalities in Acute Pancreatitis. Ann. Surg., 177:483, 1973.
3. Cameron, J. L., Zuidema, G. D. and Margolis, S.: A Pathogenesis for Alcoholic Pancreatitis. Surgery, 77:754, 1975.
4. Fallat, R. W., Vester, J. W. and Glueck, C. J.: Suppression of Amylase Activity by Hypertriglyceridemia. JAMA, 225:1331, 1973.
5. Farmer, R. G., Winkelman, E. I., Brown, H. B. and Lewis, L. A.: Hyperlipoproteinemia and pancreatitis. Am. J. Med., 54:161, 1973.
6. Fredrickson, D. S. and Lees, R. S.: Familial hyperlipoproteinemia. *In* Stanbury, J. B., Wyngaarden, J. B. and Fredrickson, D. S.; (eds): The Metabolic Basis of Inherited Disease, Second Edition. New York, McGraw-Hill, Chapter 22, 1966.
7. Glueck, C. J., Scheel, D., Fishback, J. and Steiner, P.: Estrogen-induced Pancreatitis in Patients with Previously Covert Familial Type V Hyperlipoproteinemia. Metabolism, 21:657, 1972.
8. Greenberg, B. H., Blackwelder, W. C. and Levy, R. I.: Primary Type V Hyperlipoproteinemia: A Descriptive Study in 32 Families. Ann Intern. Med., 87:526, 1977.
9. Greenberger, N. J., Hatch, F. T., Drummey, G. D. and Isselbacher, K. J.: Pancreatitis and Hyperlipemia: A Study of Serum Lipid Alterations in 25 Patients with Acute Pancreatitis. Medicine, 45:161, 1966.
10. Hatch, F. T. and Lees, R. S.: Practical Methods for Plasma Lipoprotein Analysis. Adv. Lipid Res., 6:1, 1968.
11. Havel, R. J.: Pathogenesis, Differentiation, and Management of Hypertriglyceridemia. Adv. Intern. Med., 15:117, 1969.
12. Lees, A. M., McCluskey, M. A. and Lees, R. S.: Results of Colestipol Therapy in Type II Hyperlipoproteinemia. Atherosclerosis, 24:129, 1976.
13. Lees, R. S. and Hatch, F. T.: Sharper Separation of Lipoprotein Species by Paper Electrophoresis in Albumin-containing buffer. J. Lab. Clin. Med., 61:518, 1963.
14. Lees, R. S., Wilson, D. E., Schonfeld, G and Fleet, S.: The Familial Dyslipoproteinemias. Prog. Med. Genet., 9:237, 1973.
15. Lesser, P. B. and Warshaw, A. L.: Diagnosis of Pancreatitis Masked by Hyperlipemia. Ann. Int. Med., 82:795, 1975.
16. Saharia, P., Margolis, S., Zuidema, G. D. and Cameron, J. L.: Acute Pancreatitis with Hyperlipemia: Studies with an Isolated Perfused Canine Pancreas. Surgery, 82:60, 1977.
17. Scott, W. H., Jr., Dean, R. H., LeQuire, V. et al.: Alter-

ations in Plasma Lipid Concentration in Normal and Hyperlipidemic Patients with Morbid Obesity Before and After Jejunoileal Bypass. Am. J. Surg., 135:341, 1978.

18. Wang, C., Aldersburg, D. and Feldman, E. B.: Serum Lipids in Acute Pancreatitis. Gastroenterology, 36:832, 1959.

19. Warshaw, A. L., Bellini, C. A. and Lesser, P. B.: Inhibition of Serum and Urine Amylase Activity in Pancreatitis with Hyperlipidemia. Ann. Surg., 182:72, 1975.

20. Wilcoxon, F.: Individual Comparisons by Ranking Methods. Biometrics Bull., 1:80, 1945.

DISCUSSION

DR. H. WILLIAM SCOTT, JR. (Nashville, Tennessee): For many years, we have all recognized that patients with hyperlipemia had a tendency toward attacks of pancreatitis, and until recently I, for one, had never had any concept of how or why this relation should exist. I hope Dr. George Zuidema, or his associate, Dr. John Cameron will summarize the work they have done at Hopkins, which supports the etiologic role of triglyceride elevations in plasma and the release by pancreatic lipase of free fatty acid from the triglyceride at the acinar level, and that this is likely the pathogenic mechanism of the pancreatitis.

We have had no opportunity to use jejunoileal or partial ileal bypass in patients with hyperlipemic abdominal crises or pancreatitis. The authors have done a real service in emphasizing the prompt response of pain to lowering triglyceride below 2000 mg/dl by the several treatments they have used, and the importance of avoiding extensive and expensive invasive studies, including operative procedures.

I would like to ask Dr. Miller if he has any good alternatives in etiology or pathogenesis for the pancreatitis, other than the splitting of triglycerides with release of the free fatty acids into the pancreatic acinar cells, and what could be the cause of the pain, Dr. Miller, if it is not pancreatitis? Since the elevations in triglyceride level seem to suppress amylase, could not all the pain manifestations represent subclinical, as well as clinical, grades of pancreatitis?

DR. HENRY BUCHWALD (Minneapolis, Minnesota): I want to add three patients to this reporting of cases.

We have performed partial ileal bypass, or one-third intestinal bypass, on three individuals with pancreatitis and hyperlipidemia with an excellent result. Two are completely free of symptoms, and one has had a marked mitigation of symptoms.

DR. GEORGE D. ZUIDEMA (Baltimore, Maryland): As you know, we have been interested in patients with pancreatitis associated with hyperlipoproteinemia, and for this reason I think that our approach to the problem would probably be somewhat different in terms of understanding the phenomenon which was discussed here this morning.

(slide) In our hospital, between 90 and 95% of patients entering with pancreatitis have their problem on the basis of alcohol ingestion. One thing I would like to demonstrate is that not all of these patients are heavy users of alcohol, but there is an entire spectrum in terms of utilization.

(slide) This shows that in our experience with patients with hyperlipoproteinemia the spectrum of pancreatitis ranged from mild to severe, so that there is a wide variety of patients entering with all types of pancreatitis, not only the most difficult type to handle.

(slide) This slide shows that of 31 patients admitted with pancreatitis and hyperlipoproteinemia—23, more than two-thirds, had a normal serum amylase level on admission. Five of these levels subsequently elevated, but only about one patient in four had an amylase elevation on admission.

(slide) This slide shows the results of lipid determinations in 48 patients on 57 hospital admissions, emphasizing the repeated aspect of the problem here. Ten of these patients had hyperlipemic serum, lactescent serum, and nine patients had elevated triglycerides in the range above normal but below that 600 mg/dl necessary to produce lactescent serum. Therefore, 40% of our patients had some abnormality of their triglycerides, levels and 57% had elevated free fatty acid levels.

To summarize our experience, then, we feel that a significant percentage of patients with acute pancreatitis have hyperlipoproteinemia and normal amylase levels on admission.

(slide) The next slide shows a flow sheet we have proposed, which might explain this relationship in that the patients under discussion and, I suspect, in some degree the patients that Dr. Miller is discussing as well have either a clinical or subclinical defect in lipid metabolism, and when stimulated by alcohol ingestion have increases the triglyceride levels and the chylomicrons in the blood. These, then, are activated locally by pancreatic lipase, with free fatty acid release, with acinar damage, microthrombi, and ischemia. Thus, we believe that there is a demonstrable relationship with pancreatitis.

There are four brief points upon which I would like Dr. Miller to comment. First of all, we would appreciate having some more information about the hyperlipemic patients in his group. From the ages and from the age of onset of their difficulties, it would appear that these are patients with acquired hyperlipemia, and if this is so, some information regarding the etiology of the hyperlipemia, and possibly information about a contributing factor, would be helpful.

Secondly, it would appear that the authors have a restricted definition of pancreatitis, seeming to require amylase elevation, a fall in serum calcium, fat necrosis present at operation and substantial fluid requirements. The more we see of pancreatitis, the more we realize that it can occur in milder forms, and, indeed, probably the milder forms of pancreatitis are the most common.

Thirdly, I would like to comment on the term "hyperlipemic abdominal crisis" to explain abdominal pain without amylase elevation. I must raise the question as to whether this is, indeed, a new syndrome, or, in most instances, whether we are not seeing a mild form of pancreatitis without deviation in serum amylase levels.

The final point the authors have made is the importance of avoiding unnecessary operations. I believe that these patients' being considered to have mild pancreatitis, would be a great help in avoiding unwarranted laparotomies.

I am afraid, therefore, that I remain somewhat unconvinced but believe that these patients should be considered to have mild pancreatitis until it is proved otherwise.

In terms of Dr. Scott's question about what to do when the lipid chemists are not on duty at night, the simplest thing is to draw a tube of blood and tape it to the side of the bed; if you have lactescent serum, you know that triglyceride levels are in excess of 600 mg/dl.

DR. ARNOLD MILLER (Closing discussion): We do not know whether this is pancreatitis or abdominal pain of some other cause. What we did try to do was define pancreatitis on a clinical basis, and we were not able to do this in this group of patients.

In answer to Dr. Zuidema first, none of our patients, first of all, was an alcoholic. All patients were proved familial Type V patients and therefore did not have hyperlipemia of an acquired type.

The term "hyperlipemic abdominal crisis" was used to try to differentiate what we consider clinical pancreatitis and this other form of abdominal pain. One of the causes of the other form of abdominal pain which we have noted is the tremendous, rapid organomegaly causing tenderness. On the other hand, at operation on some of these patients there seems to be some type of serosal inflammation and increased free fluid without any evidence of edema of the pancreas or other sign of pancreatitis.

We believe we are dealing with two different entities. We hope that with more finite metabolic tests that will define pancreatitis, or show pancreatitis at an earlier stage, we may be able to differentiate between the two even more clearly.

Surgical Decision Making

The Reliability of Clinical Judgment

IRA M. RUTKOW, M.D., M.P.H., ALAN M. GITTELSOHN, Ph.D., GEORGE D. ZUIDEMA, M.D.

Elective surgery second opinion programs are predicted on strict acceptance of the accuracy of the consultant's surgical judgment. The reliability and reproducibility of clinical judgment, therefore, become basic to the effectiveness of such programs. This aspect, however, has received little attention. We report a randomized and controlled survey of surgical specialists which defines agreement/disagreement patterns in surgical decision-making for seven elective surgical procedures. For each disease process, four case histories, including at least one control, were developed by specialty panels of physicians. The case summaries described fictional patients who were seeking professional consultation. The histories were mailed to a random sample of Board-certified specialists from the State of Maryland and the District of Columbia. The response rate was approximately 80% for all five specialties. The respondents were asked to indicate whether they would (Yes) or would not (No) perform the surgical procedure in question. Factual knowledge was not sought, but instead the application of that knowledge and experience to decide on the need for surgical intervention. By comparing the responses for each case history, the agreement/disagreement patterns of inter-observer surgical judgment were determined. Analysis of the data revealed a marked divergence of opinion concerning the need for surgery.

		Case 1	Case 2	Case 3	(control) Case 4
Breast Surgery	Yes	58%	36%	85%	99%
	No	42	64	15	1
Varicose vein surgery	Yes	36	91	12	95
	No	64	9	88	5
Cholecystectomy	Yes	82	48	80	98
	No	18	52	20	2
Hysterectomy	Yes	11	65	25	96
	No	89	35	75	4
T & A	Yes	19	54	40	100
	No	81	46	60	0
				(control)	
Cataract extraction	Yes	88	51	100	0
	No	12	49	0	100
Prostatectomy	Yes	22	22	100	0
	No	78	78	0	100

From the Department of Surgery and Departments of Biostatistics and Health Services Administration, The Johns Hopkins University School of Medicine and the School of Hygiene and Public Health, Baltimore, Maryland

The significant point of this study is that surgical judgment differs to a major degree from one surgeon to the next. In a second-opinion program the number of consultants needed to provide a reliable clinical decision probably exceeds the number who are logistically available and that the patient would be willing to visit. Surgical decision-making is a semi-exact scientific process, and it is unreasonable to expect exact answers to clinical problems.

THE SURGICAL DECISION MAKING process and factors which affect it have been the subjects of several recent reports.[39] As the surgical sciences currently consume the largest single share of the American health care dollar and because the surgical operation is easily identified, classified and studied, it is likely that other studies will be performed. The United States has rates of performance for some common elective operations which are two and three times those of other countries.[5,27,35] The significance of this finding in view of differing health care delivery systems remains uncertain.[31] Of the various explanations offered, the most important are said to be social and economic conditions,[2,6,9,18,36,40] organizational plans[12] and geographical and demographical factors.[11,19,26,45,46] Also suggested are different styles of therapeutic management, including variations in surgical attitudes and philosophies toward the treatment of certain disease processes.[15]

One method which has recently been introduced as a means to help control the increasing number of surgical procedures and resultant health care expenditures has been elective surgery second opinion programs.[16,29,30] They are designed to be consumer-oriented and are meant to screen those elective operations which might otherwise be deferred or prevented without jeopardizing the general health and well-being

---

Presented at the Annual Meeting of the American Surgical Association, Hot Springs, Virginia, April 26–28, 1979.

Reprint requests: Dr. Ira M. Rutkow, Department of Surgery, The Johns Hopkins Hospital, Baltimore, Maryland 21205.

Supported in part by funds from the Robert Wood Johnson Foundation. Dr. Rutkow is a Robert Wood Johnson Clinical Scholar.

0003-4932/79/0900/0409 $01.05 © J. B. Lippincott Company

of the individual. Whether they are truly beneficial for the patient and ultimately cost effective remains to be determined.

Second opinion programs are predicated on the accuracy of the consultant's surgical judgment. The measurement of the reliability and reproducibility of clinical decision making, therefore, becomes basic to the effectiveness of such programs. This aspect, however, had received little attention prior to the introduction of second opinion methodology. Attempts at defining and measuring surgical judgment have always proved to be difficult.[22] It is known that skilled surgeons examining the same patient may disagree with regard to the physical findings, interpretation of laboratory results and overall treatment plan. Such disagreements only reflect the imperfect reliability of clinical methods and information gathering.

This study was undertaken to examine the process by which surgeons formulate clinical opinions. We report a systematically randomized and controlled survey of general surgeons and surgical specialists which attempts to measure agreement-disagreement patterns in surgical decision making. The study also examines the effects of six educational, financial and organizational factors on the decision to perform elective surgery.

Methods and Procedures

Four case histories were developed by specialty panels of surgeons from The Johns Hopkins Hospital for each of seven different disease processes. They include breast and varicose vein surgery, cholecystectomy, hysterectomy, tonsillectomy and adenoidectomy, cataract extraction and prostatectomy. The surgical vignettes describe fictional patients with ordinary clinical problems who are seeking professional consultation for their situation. Deliberately difficult and involved clinical summaries were avoided.

For three of the specialties (general surgery, obstetrics and gynecology and otorhinolaryngology) at least one of the case histories was designed to represent a pathological process in definite need of surgical intervention. This is referred to as the positive control case history. In addition, for ophthalmology and urology a vignette without definite need for surgery was added, the negative control case history. The remaining histories are called test cases. The vignettes allow for implicit judgments to be made. These rely on the subjective opinion of the individual judge, and no predetermined criteria are utilized.[3] A representative general surgical "cholecystectomy" case history follows:*

History

A 53-year-old woman is under evaluation for vague intermittent abdominal pain located in the right upper quadrant with occasional epigastric involvement. She states that the pain seems to be aggravated by ingestion of fatty foods, although it does come about even if a meal is not consumed. The discomfort lasts from 60–90 minutes and has been noted to radiate to the right shoulder and scapula. The pain was first noted six months ago, and at that time a double dose oral cholecystogram had faintly visualized, an intravenous cholangiogram was within normal limits and an upper gastrointestinal series, barium enema and intravenous pyelogram were all unremarkable. She was started on an antacid regimen which provided some temporary relief, but over the past two months the discomfort had considerably worsened. Both her past medical history and family history were unremarkable. She presents now for further evaluation of this abdominal distress and notes the recent onset of eructation and increased flatulence.

Physical examination. The current physical examination is within normal limits, although you have evaluated her in the past when she did have epigastric and right upper quadrant tenderness with minimal guarding but no rebound. At that time Murphy's sign was questionably elicited.

Laboratory data. Repeat oral cholecystogram again demonstrates faint visualization, and the intravenous cholangiogram, upper gastrointestinal series and barium enema are all within normal limits. Ultrasound was also considered unremarkable.

Clinical impression—Cholecystitis? Based on the above information do you feel at this time that a) cholecystectomy is indicated, b) cholecystectomy is not indicated.

Comments

Independent and systematic random samples of general surgeons and surgical specialists were drawn from state address rosters listed in the *Directory of Medical Specialists, 18th Edition—1977–1978.*† The sample was composed solely of diplomates of the respective specialty boards.

The appropriate case histories were mailed to 155 general surgeons, 33% systematic random sample; 135 obstetricians and gynecologists, 25% systematic random sample; 100 otorhinolaryngologists, 70% systematic random sample; 115 ophthalmologists, 50% systematic random sample; and 100 urologists, 70% systematic random sample. All physicians surveyed were from the State of Maryland and the District of Columbia.

The surgeons were asked to evaluate the case history as if they were a second opinion consultant and to indicate whether they would or would not perform the procedure under question. Factual knowledge was not sought but instead the application of knowledge and experience to decide on the need for surgical intervention. In addition to the yes/no responses the respondents also provided personal and professional background information on six educational, financial and organizational factors. These included 1) year of Board certification; 2) graduation from either an American/Canadian versus foreign medical school; 3 and 4) type of hospital where clinical training took place and where most operations are currently performed; 5) structure of the practice and 6) method of financial reimbursement for surgery. In all instances, anonymity was assured for the individual surgeon, although numerical coding of the answer sheet was completed so that nonrespondents could be identified and characterized. The first mailing took place in March 1978, with a follow-up to nonrespondents in mid-April 1978.

---

* The remaining vignettes are available on request.

† Published by Marquis Who's Who, Chicago, Illinois.

Analysis of the data was completed by comparing the total yes/no responses for each case history and determining the agreement/disagreement patterns of interobserver surgical judgment. Any divergence of opinion concerning the need or lack of need for surgical intervention would indicate relative difficulty in reaching a stable clinical decision. This can be utilized to represent one measure of the general reliability of clinical decisions with regard to elective surgery.

The six educational, financial and organizational factors were analyzed using chi-square statistical tests to determine if any significant trends or correlations between these variables and a surgeon's willingness to perform surgery were present. To accomplish this the total number of yes responses to the three test case histories were obtained for each procedure. This total was then selectively examined for the various subclasses of the six factors.

TABLE 1. *Yes/No Responses to the Case Histories*

		Case 1 (%)	Case 2 (%)	Case 3 (%)	Case 4 (%)
					(Control)
Breast surgery (92)	Yes	58	36	85	99
	No	42	64	15	1
Varicose vein surgery (90)	Yes	36	91	12	95
	No	64	9	88	5
Cholecystectomy (90)	Yes	82	48	80	98
	No	18	52	20	2
Hysterectomy (99)	Yes	11	65	25	96
	No	89	35	75	4
T&A (68)	Yes	19	54	40	100
	No	81	46	60	0
				(Control)	
Cataract extraction (85)	Yes	88	51	0	100
	No	12	49	100	0
Prostatectomy (67)	Yes	22	22	0	100
	No	78	78	100	0

Numbers in parentheses indicate the number of surgeons.

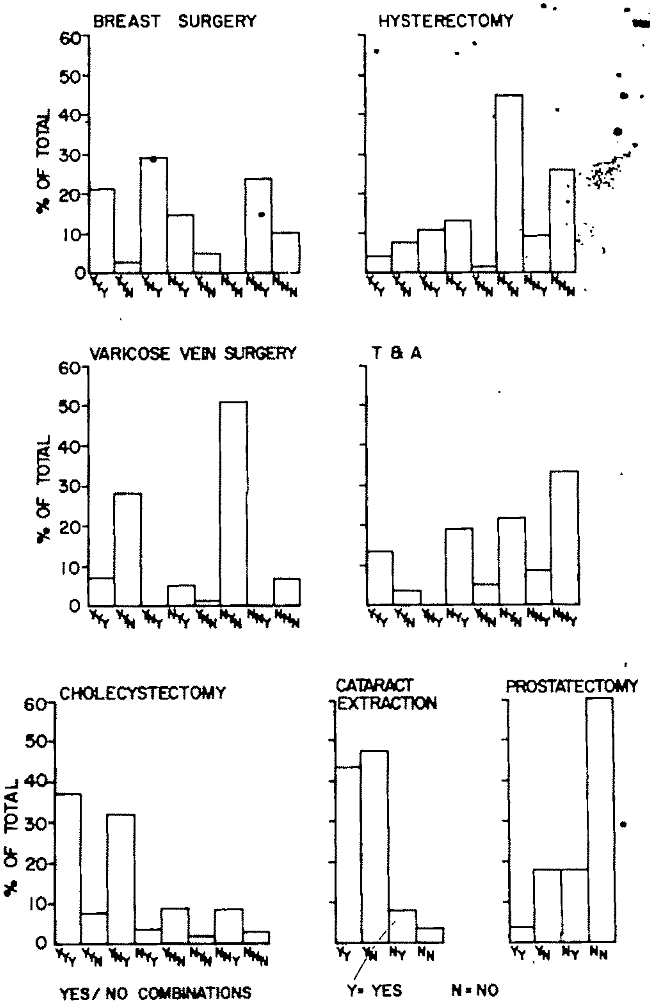


FIG. 1. The yes/no combinations to the case histories reveal marked patterns of disagreement for all seven surgical procedures.

Results

Response Rates

For each specialty, approximately 15% of the overall sample population had retired, were deceased or could not be located. Of the remainder, the response rates were general surgery, 78% (n = 92); obstetrics and gynecology, 80% (n = 99); otorhinolaryngology, 83% (n = 68); ophthalmology, 85% (n = 85); and urology, 79% (n = 67).

Patterns of Agreement/Disagreement in Surgical Decision Making

Analysis of the yes/no responses to the test case histories revealed a marked divergence of opinion concerning the need for surgery. Of the 19 test cases only one showed greater than 90% agreement among the respondents. Seven demonstrated between 80 and 89% agreement, three between 70% and 79%, four from

TABLE 2. *Graduates of American/Canadian Versus Foreign Medical Schools*

Procedure	Yes Responses to the Test Case Histories	
	American/ Canadian (%)	Foreign (%)
Breast surgery	(80) 60	(12) 53
Varicose vein surgery	(79) 45	(11) 55
Cholecystectomy	(79) 74	(11) 70
Hysterectomy	(80) 35	(19) 30
T&A	(61) 38	(7) 33
Cataract extraction	(82) 70	(3) 67
Prostatectomy	(60) 23	(7) 21

Numbers in parentheses indicate number of surgeons.

TABLE 3. *Decade of Board Certification*

Procedure	Yes Responses to the Test Case Histories			
	Before 1950 (%)	1950–1959 (%)	1960–1969 (%)	After 1970 (%)
Breast surgery	(9) 52	(23) 58	(31) 58	(29) 64
Varicose vein surgery	(9) 56	(22) 45	(30) 49	(29) 41
Cholecystectomy	(9) 59	(22) 59	(30) 78	(29) 74
Hysterectomy	(10) 27	(21) 32	(39) 38	(29) 32
T&A	(11) 39	(13) 38	(17) 31	(27) 41
Cataract extraction	(5) 80	(10) 65	(30) 68	(40) 70
Prostatectomy	(7) 21	(8) 31	(16) 25	(36) 19

Numbers in parentheses indicate number of surgeons.

60 to 69% and four between 50 and 59%. In all instances the control case histories obtained response rates with 95% or greater agreement (Table 1).

Detailed analysis of each procedure reveals further patterns of disagreement. Utilizing the three test cases for each procedure, a total of eight different yes/no response combinations are possible for the general surgeon, obstetrician and gynecologist and otorhinolaryngologist. These range from yes/yes/yes for the three cases to all no's. Similarly, a total of four different yes/no combinations are possible for the ophthalmologist and urologist, since they received only two case histories. Marked patterns of disagreement are noted for all the procedures (Fig. 1).

Educational, Financial and Organizational Factors and the Decision to Perform Surgery

The six personal and professional background factors were analyzed for the presence of any significant trends or correlations among the variables and/or a surgeon's willingness to perform surgery. No consistent patterns or statistically significant correlations were found to indicate a positive or negative effect on the surgical decision making process (Tables 2–7).

Discussion

Agreement/Disagreement Patterns in Surgical Decision Making

Observer variability in the examination of patients, interpretation of laboratory results and planning of therapeutic modalities is an accepted phenomenon. However, it is only recently that this has been of interest to investigators. Koran in a review of studies on interobserver agreement stated, "the unreliability of clinical methods and data and the physician's judgments regarding indicated treatments must be acknowledged in any fair review process. Moreover, the limited dependability of physician's evaluations of quality of care suggests that the reliability and accuracy of the reviewing process itself should be repeatedly assayed."[21] The opposite viewpoint is taken by Feinstein, who states, "despite many minor variations and some major disagreements, experienced clinicians can generally reach good agreement with themselves or with other clinicians."[13]

The concept of observer error or variation is not new.[20] In 1646, Sir Thomas Brown in his book *Pseudodoxia Epidemica* described several sources of human error.[4] In the early 1930s the variability of physician

TABLE 4. *Type of Hospital at Which Clinical Training Took Place*

Procedure	Yes Responses to the Test Case Histories			
	University (%)	University Plus Community (%)	Community (%)	Public Health, Armed Forces and Veterans Admin. (%)
Breast surgery	(55) 63	(13) 56	(14) 50	(10) 57
Varicose vein surgery	(54) 41	(13) 62	(13) 44	(10) 57
Cholecystectomy	(54) 70	(13) 72	(13) 62	(10) 77
Hysterectomy	(45) 34	(25) 32	(18) 37	(11) 30
T&A	(45) 38	(9) 26	(5) 27	(9) 56
Cataract extraction	(51) 69	(10) 60	(7) 50	(17) 85
Prostatectomy	(45) 19	(3) 0	(4) 13	(15) 40

Numbers in parentheses indicate number of surgeons.

TABLE 5. *Type of Hospital at Which the Surgeon Currently Operates*

	Yes Responses to the Test Case Histories			
Procedure	University (%)	Community Plus House Staff (%)	Community Plus No House Staff (%)	Public Health, Armed Forces and Veterans Admin. (%)
Breast surgery	(16) 69	(53) 57	(17) 61	(6) 50
Varicose vein surgery	(16) 33	(52) 49	(16) 52	(6) 39
Cholecystectomy	(16) 69	(52) 69	(16) 79	(6) 56
Hysterectomy	(14) 31	(63) 35	(13) 23	(9) 41
T&A	(13) 28	(30) 40	(15) 38	(10) 43
Cataract extraction	(15) 57	(46) 68	(15) 80	(9) 78
Prostatectomy	(11) 32	(32) 17	(20) 23	(4) 38

Numbers in parentheses indicate number of surgeons.

judgment was studied when a random population of 1000 school children from New York City were chosen to undergo examination for tonsil disease.[1] Of the 1000 students, 611 had had a previous tonsillectomy and adenoidectomy (T&A). Of the remaining 389, 174 were told they needed to have their tonsils removed at once. The 215 with so-called healthy tonsils were examined by a second group of school physicians who felt that 99 of them were in need of T&A. Still, another group of doctors examined the remaining 116 children of whom an additional 51 were recommended for removal of their tonsils. By the end of four different physician examinations only 65 out of the original 1000 children had tonsils which were not removed or recommended for removal. Observer variation with regard to the choice of a treatment plan was clearly present.

Although increasing information is becoming available on agreement/disagreement patterns in the nonsurgical fields of medicine,[7,8,14,34] there have been few such studies within the surgical sciences. This is not surprising, for unlike the medical specialties in which the results of a diagnostic test can be reviewed by a large number of physicians, it is more difficult to personally evaluate the surgical patient by sufficiently large numbers of surgeons.

In the 1950s and 1960s a number of articles appeared in the surgical literature citing the effectiveness of hospital tissue committees in raising surgical standards.[41,43,44] They documented significant levels of clinical disagreement among surgeons. Nonetheless, the tissue committee approach was utilized in attempts to decrease overall surgical rates without changing morbidity and mortality. By the 1970s, studies of the surgical decision making process were being put on a more scientific basis. DeRouville reported on the flaws inherent in surgical review programs employing multiple assessors of care quality and which rely on peer judgment for evaluation of that care.[10] It was concluded that surgical judges tend to change self-imposed criteria for judging the quality of care, and as a result the concept of reproducibility of surgical opinion may not be valid. A 1972 study by Richardson cast doubt on the validity and reliability of uncontrolled peer judgments.[37] He showed that surgeons consistently differed in the degree of harshness or permissiveness when judging charts, that they depended on different aspects of clinical care to make final judgments of the quality of care and that the number of surgeons needed to reach a stable judgment of care quality exceeded the number logistically available to meet the demands of third

TABLE 6. *Structure of Practice*

	Yes Responses to the Test Case Histories				
Procedure	Solo and Hospital Based (%)	Single Specialty (%)	Multi-specialty (%)	Academic (%)	Public Health, Armed Forces and Veterans Admin. (%)
Breast surgery	(53) 56	(20) 63	(3) 78	(11) 67	(5) 53
Varicose vein surgery	(52) 43	(20) 55	(3) 56	(10) 47	(5) 40
Cholecystectomy	(52) 66	(20) 75	(3) 78	(10) 77	(5) 73
Hysterectomy	(43) 33	(40) 33	(3) 22	(4) 42	(9) 41
T&A	(28) 32	(20) 50	(2) 0	(8) 29	(10) 43
Cataract extraction	(53) 73	(17) 62	(1) 50	(5) 40	(9) 83
Prostatectomy	(23) 22	(36) 21	(0) 0	(4) 25	(4) 38

Numbers in parentheses indicate number of surgeons.

TABLE 7. *Financial Reimbursement for Surgery*

	Yes Responses to the Test Case Histories			
Procedure	Fee-for-service (%)	Fee-for-service Plus Some Salary (%)	Salaried Plus Some Fee-for-service (%)	Salaried (%)
Breast surgery	(51) 52	(16) 75	(9) 67	(16) 65
Varicose vein surgery	(50) 51	(15) 47	(9) 33	(16) 40
Cholecystectomy	(50) 69	(15) 76	(9) 70	(16) 67
Hysterectomy	(70) 30	(8) 46	(7) 33	(14) 43
T&A	(44) 39	(2) 50	(6) 39	(16) 31
Cataract extraction	(61) 70	(2) 75	(1) 50	(16) 69
Prostatectomy	(49) 17	(6) 33	(1) 50	(11) 36

Numbers in parentheses indicate number of surgeons.

party payers. It was estimated, for example, that 21 surgeons would be needed to produce a composite judgment of a single case with 95% levels of reliability (Fig. 2).

A recent article by Graham et al. demonstrated a significant amount of observer variation in the interpretation of physical signs in patients with ulcerative colitis.[17] A 1977 study from Great Britain documented a 45% variation between physicians in recording the presence or absence of axillary nodes in women presenting with breast lesions and a 55% discrepancy in sizing the primary lesions.[42] Three studies by Lazaro et al. have shown the extent of interobserver surgical disagreement with regard to the 1) management of arterial insufficiency of the lower extremities, 2) treatment of abdominal sepsis and 3) therapeutic considerations of cancer of the breast.[23–25] Munster et al. utilizing a questionnaire survey of all the chiefs of surgery in the Veterans Administration hospital system, was able to document a high level of disagreement concerning the indications for the use of prophylactic antibiotics in surgery.[32]

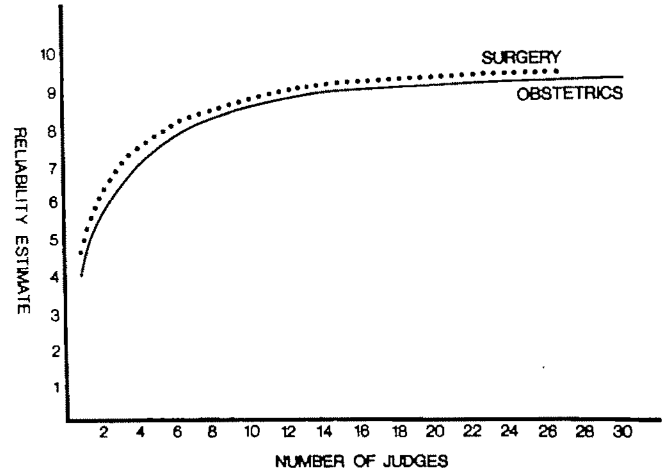


FIG. 2. Average judgment reliability change as a function of additional judges. (From Richardson, F. M.: Peer Review of Medical Care. Med. Care, 10:29, 1972, by permission.)

The most important recent development to stimulate the study of agreement/disagreement patterns in surgical decision making came from the institution of elective surgery second opinion programs.[16,29,30] They are designed to provide a means for obtaining at least one additional surgical consultation by a board-certified surgical specialist for those patients advised to undergo an elective surgical procedure. specifically, the objective was to screen those elective operations which might otherwise be deferred or prevented without jeopardizing the general health and well-being of the patient.

Although not designed to specifically measure the difference of opinion between physicians, they do, in fact, provide an imprecise but definite indication of the reliability of clinical surgical decision making. If elective surgery second opinion programs are to be predicated on strict acceptance of the accuracy of the consultant's surgical judgment, then an understanding of the reliability and reproducibility of clinical surgical judgment becomes basic to the effectiveness of such programs. Similarly, the reasons why a patient accepts or rejects a physician's opinion must be clarified. McCarthy and Finkel have shown that over 20% of the patients who received a nonconfirmation from a second opinion consultant with regard to the necessity for surgery still proceeded to undergo surgery within a 12-month period.[30] On the other hand, over 10% of the patients who received positive confirmation for surgery from both the initial screening physician and the second opinion consultant are reported to have neither received further medical treatment nor undergone the recommended operation. If levels of disagreement are known to be high and patient compliance poor, why obtain only a second opinion? Perhaps it would be better to have third, fourth and fifth opinions?

This investigation shows that for many common elective surgical situations the opinions rendered will differ to a major degree from one surgeon to the next. The reliability of their observations or clinical opinions is different from their accuracy. The decisions of two surgeons may agree, that is, be reliable with one another, and yet be incorrect with regard to the actual standard of accuracy. The purpose of this report is to measure to what degree surgeons will agree or disagree with one another. It should also make both physician and lay person aware that there is significant variation in surgical decision making.

It remains an open question whether the magnitude of observer variation shown in this report reflects specific difficulties in the surgical decision making process or if it highlights some more general problem of which the clinician may be unaware. Either way, it is neither the magnitude nor the presence of the variation that is important but the effect which they may have on the diagnostic process and on the physician engaged in that process.

Some conclusions are known about factors which influence physician agreement/disagreement.[21] The more surgeons involved, the more diagnoses to consider, and the less severe the disease process under consideration, the lower the interobserver agreement rate will be.[21] Reliability regarding the normal situation is usually higher than that concerning abnormality. Agreement for yes/no judgments will tend to be higher than agreement for continuous or qualitative scales. Finally, physicians with more training relative to the judgments under consideration will agree more often than physicians with less training. Two other less obvious facts are known: 1) when levels of agreement expected by chance are taken into account (*i.e.*, per cent maximum standard deviation), the ability of physicians to agree is substantially less than when measured by indices that do not correct for chance accord (*i.e.*, overall per cent agreement) and 2) physician judgments regarding quality of care may be only poorly related to the actual outcome of care.

The findings from this investigation must be viewed with some caution. First, the important personal aspect of the patient/physician contact is not present in such vignettes. This relationship is known to have an important role in the surgical decision making process, and to this extent the case histories do not represent real-life situations. This criticism, however, is also applicable to similar investigations employing chart reviews, tissue committees, utilization reviews and audits. Secondly, when questionnaires come from academic institutions or professional organizations, a bias may influence some respondents to recommend what they construe to be more acceptable criteria. Finally, the study was completed in only one distinct geographical area of the United States. Whether similar patterns of agreement/disagreement exist in other sections of this country remains to be determined.

Educational, Financial and Organizational Factors and the Decision to Perform Elective Surgery

The incidence of operative rates in the USA has undergone considerable study over the past decade. The USA has rates of surgery which are higher than those of other countries with similar economies and health care delivery systems.[5,27,35] Discharge data from the National Center for Health Statistics show an unprecedented increase in surgical rates for the years 1971–1975.[33] The 1971 rate of 78 in-hospital procedures per 1000 population rose to 96 in 1975. In 1973 there were a total of 18.5 million surgical procedures performed. This increased to 20 million by 1976.

Several factors have been thought to account for both the upward and regionally varying incidence rates of surgical procedures in this country. Among the most prominent has been the suggestion that the absolute number of surgical practitioners may be the ultimate cause of high surgical rates. In 1970, Bunker reported that Americans had twice the number of operations performed on a per capita basis as did England and Canada.[5] At the same time, the USA had twice as many surgeons as did the other two countries. There have been a number of studies which show intrastate variations in operative rates which seem to correlate with the distribution of surgeons within that state.[11,26,45,46] The SOSSUS Report concluded that many physicians performing surgical procedures are not board certified and suggested that there is a need to reduce the number of surgical residency positions.[47]

Other investigations have examined various social and economic stategies and their effects on surgical rates. Bombardier and Fuchs have suggested that income has a large effect on surgical utilization with higher socioeconomic groups tending to have more operations, while more educated populations tend to have fewer surgical operations.[2] Bunker, and Brown, however, showed that the most well-informed and educated consumer, specifically the physician and his or her family, had the highest use of surgery when compared to other professional groups.[6] A study from Rhode Island pointed out that many frequently performed surgical procedures had similar rates for the high, middle and low socioeconomic groups.[40] Roos et al., in a report on T&A rates in Canada, were unable to correlate performance with such variables as physician age, place of training or specialty.[38] A recent analysis of urban/rural surgery failed to find any striking dissimilarity in the surgical health care which was delivered to the two populations.[19]

The effect of various payment mechanisms and of differing systems of health care delivery has also been studied. In 1960, Densen et al., demonstrated that in a fee-for-service versus pre-paid medical insurance plan the female surgical admissions for the fee-for-service plan were markedly higher.[9] A study from Canada documented similar findings.[18] Not all prepaid plans, however, have shown lower surgical rates. Perkoff et al., were unable to find reduced surgical admissions among a prepaid group practice population.[36] Egdahl et al., have noted the potential of fee-for-service health maintenance organizations to achieve significant decreases in hospitalization rates.[12]

These findings indicate the difficulty in explaining variances in rates of surgery in different areas. A high rate of surgery does not necessarily mean that too many procedures are being performed,[38] and a low rate may indicate that not enough surgery is being done.[31] Either way it is important that one does not make subjective value judgments concerning operative rates without careful study of the methods used to obtain the data and the variables under examination.[28]

The results of this survey have failed to find any statistically significant associations between six educational, financial and organizational factors and a surgeon's willingness to perform surgery. The previously suggested importance of certain economic incentives in determining high or low surgical rates in the United States was not documented.[15] Other possible reasons such as different patterns of surgical practice and presumed related differences in surgical judgment and philosophy should therefore be investigated before any one determinant is accepted as the major cause of increasing and regionally varying rates within this country.

The reliability of surgical judgment is undergoing increased scrutiny. Are differences in basic surgical philosophy more important than the effect of various systems of surgical health care delivery in ultimately determining operative rates? Are there differences toward inclination to operate between surgeons of different countries? Is it valid to rely upon second opinions to indicate the need for surgery or are differences in judgment between surgeons more a matter of chance than a result of scientific decision making? These questions and others need to be studied before the process of surgical decision making is fully understood.

Acknowledgments

We wish to thank Barbara H. Starfield, M.D., M.P.H. and Professor Samuel Shapiro, for their critical review of the manuscript and Beth R. Greenwald, B.A., and Helaine Wendell for their research assistance.

References

1. American Child Health Association: Physical Defects—The Pathway to Correction. Chap. VIII. School Health Influence on Tonsillectomy, 1934.
2. Bombardier, C. and Fuchs, V. R.: Socioeconomic Factors Affecting the Utilization of Surgical Operations. N. Engl. J. Med., 288:699, 1977.
3. Brooks, R. H. and Appel, F. A.: Quality-of-Care Assesment: Choosing a Method of Peer Review. N. Engl. J. Med., 288:1323, 1973.
4. Brown, T.: *Pseudodoxia Epidemica*. London, 1646.
5. Bunker, J. P.: Surgical Manpower—A Comparison of Operations and Surgeons in the United States, England and Wales. N. Engl. J. Med., 282:135, 1970.
6. Bunker, J. P. and Brown, B. W., Jr.: The Physician-Patient as an Informed Consumer of Surgical Services. N. Engl. J. Med., 290:1051, 1974.
7. Conn, H. O., Mitchell, J. R. and Brodoff, M. G.: A Comparison of the Radiologic and Esophagoscopic Diagnosis of Esophogeal Varices. N. Engl. J. Med., 265:160, 1961.
8. Davies, L. G.: Observer Variation in Reports on Electrocardiograms. Br. Heart J., 20:153, 1958.
9. Densen, P. M., Jones, E. W., Balamuth, E. and Shapiro, S.: Prepaid Medical Care and Hospital Utilization in a Dual Choice Situation. Am. J. Public Health, 50:1710, 1960.
10. deRouville, W. H.: Peer Review in Biliary Tract Surgery. N. Y. State J. Med., 71:1544.
11. Detmer, D. E. and Tyson, T. J.: Regional Differences in Surgical Care Based Upon Uniform Physician and Hospital Discharge Abstract Data. Ann. Surg., 187:166, 1978.
12. Egdahl R. H., Taft, C. H., Friedland, J. and Linde, K.: The Potential for Organizations of Fee-for-Service Physicians for Achieving Significant Decreases in Hospitalization. Ann. Surg., 186:388, 1977.
13. Feinstein, A. R.: Clinical Judgment. Baltimore, Williams & Wilkins Co., 1967.
14. Geffen, N., Danborough, A., deDombal, F. T. et al.: Signs of Ulcerative Colitis: Assessment of Their Reliability by Means of Observer Variation Studies. Gut, 109:19, 1973.
15. Gittelsohn, A. M. and Wennberg, J. E.: On the Risk of Organ Loss. J. Chronic Dis., 29:527, 1976.
16. Grafe, W. R., McSherry, C. K., Finkel, M. L. and McCarthy, E. G.: The Elective Surgery Second Opinion Program. Ann. Surg., 188:323, 1978.
17. Graham, N. G., deDombal, F. T. and Goligher, J. C.: Reliability of Physical Signs in Patients with Severe Attacks of Ulcerative Colitis. Br. Med. J. 1:746, 1971.
18. Hastings, J. E. F., Mott, F. D., Barclay, A. and Hewitt, D.: Prepaid Group Practice in Sault Ste. Marie, Ontario. Med. Care, 11:91, 1973.
19. Kane, R. L. and Olsen, D. M.: Giving and Getting Surgery in Utah: An Urban-Rural Comparison. Surgery, 83:375, 1978.
20. Kilpatrick, G. S.: Observer Error in Medicine. J. Med. Educ., 38:38, 1963.
21. Koran, L. M.: The Reliability of Clinical Methods, Data and Judgments. N. Engl. J. Med., 293:642, 1975.
22. Laufman, H.: Some Thoughts on Surgical Judgment. Surg. Clin North Am., 1169, 1967.
23. Lazaro, F. J., Rush, B. F. and Alessi, A. A.: Controversies in the Management of Arterial Insufficiency of the Lower Extremities—A Questionnaire Course. J. Med. Soc. N.J. 73:45, 1976
24. Lazaro, F. J., Rush, B. F., Jr. and Dolan, J.: Controversies in the Management of Abdominal Sepsis—A Questionnaire course. J. Med. Soc. N.J., 74:234, 1977.
25. Lazaro, E. J., Rush, B. F., Jr., Landor, J. and Grimes, E. L.: Controversies in the Management of Cancer of the Breast—A Questionnaire Course. J. Med. Soc. N.J., 74:943, 1977.

26. Lewis, C. E.: Variations in the Incidence of Surgery. N. Engl. J. Med., 281:880, 1969.
27. Logan, R. F. L. and Eimerl, T.: Case Loads in Hospital and General Practice in Several Countries. Milbank Mem. Fund., Q., 43:302, 1965.
28. LoGerfo, J. P.: Variations in Surgical Rates: Fact vs. Fantasy. N. Engl. J. Med., 297:387, 1977.
29. McCarthy, E. G. and Finkel, M. L.: Second Opinion Elective Surgery Programs: Outcome Status Over Time. Med. Care, 16:984, 1978.
30. McCarthy, E. G. and Widmer, G. W.: Effects of Screening by Consultants on Recommended Elective Surgical Procedures. N. Engl. J. Med., 291:1331, 1974.
31. Moore, F. D.: What Puts the Surge in Surgery? N. Engl. J. Med., 283:162, 1970.
32. Munster, A. M., Weiner, J. and Gibson, G.: Prophylactic Antibodies in Surgery. JAMA, 241:717, 1979.
33. National Center for Health Statistics: Surgical Operations in Short-Stay Hospitals, 1965, 1968, 1971, 1973, 1976. Washington, U.S. Dept. HEW, Government Printing Office.
34. Norden, C., Phillips, E., Levy, P. et al.: Variation in Interpretation of Intravenous Pyelograms. Am. J. Epidemiol, 91:155, 1970.
35. Pearson, R. J. C., Smedby, B. and Berfenstam, R.: Hospital Case Loads in Liverpool, New England and Uppsala: An International Comparison. Lancet, 2:559, 1968.
36. Perkoff, G. T., Ballinger, W. F., Turner, J. K. and Kahn, L.: Lack of Effect of an Experimental Group Practice on Utilization of Surgical Care. Surgery, 77:619, 1975.
37. Richardson, F. M.: Peer Review of Medical Care. Med. Care, 10:29, 1972.
38. Roos, N. P., Roos, L. L. and Henteleff, P. D.: Elective Surgical Rates: Do High Rates Mean Lower Standards? N. Engl. J. Med., 297:360, 1977.
39. Rutkow, I. M. and Zuidema, G. D.: "Unnecessary Surgery": An Update. Surgery, 84:671, 1978.
40. Scott, H. D. and Mackie, A.: Decisions to Hospitalize and Operate: A Socioeconomic Perspective in an Urban State. Surgery, 77:311, 1975.
41. Sharpe, H. R.: The Effect of a Tissue Committee on Appendectomy in a General Hospital. Wis. Med. J., 135:215, 1960.
42. Smiddy, F. G.: Observer Variation in Recording Clinical Data from Women Presenting with Breast Lesions. Br. Med. J., 2:1196, 1977.
43. Verda, D. J. and Platt, W. R.: The Effectiveness of the Tissue Committee at the Missouri Baptist Hospital. Bull. Am. Coll. Surg., 43:449, 1958.
44. Weinert, H. V. and Brill, R.: Effectiveness of Hospital Tissue Committee in Raising Surgical Standards. JAMA, 150:992, 1952.
45. Wennberg, J. and Gittelsohn, A. M.: Small Area Variations in Health Care Delivery. Science, 182:1102, 1973.
46. Wennberg, J. and Gittelsohn, A. M.: Health Care Delivery in Maine: Patterns of Use of Common Surgical Procedures. J. Maine Med. Assoc., 66:123, 1975.
47. Zuidema, G. D.: The Study on Surgical Services for the United States. American College of Surgeons, Chicago, 1975.

DISCUSSION

DR. C. ROLLINS HANLON (Chicago, Illinois): This is a nice analysis of the surgical decision-making process in a controlled theoretic model that indicates, as Dr. Rutkow has pointed out, the lack of scientific precision in surgical decision-making in this fictitious setting.

The authors would, as was not mentioned in the abstract, but as Dr. Rutkow has pointed out, agree that two vital components of the clinical decision-making process have been excluded from their model. These components are first, discussion between the two physicians making the recommendation, a factor of critical importance in the true consultative process, and second, the live patient, with his opinions, his questions and his participation in the surgical decision-making, was necessarily excluded from this process—not only, indeed, the patient, but his spouse, other members of the family, his relatives and his friends.

Dr. Rutkow mentioned some cautions regarding this study, and I would echo those. He did not mention that the study will be quoted inappropriately to suggest that physicians, and especially surgeons, are not certain as to what they are doing, inasmuch as the Case 2 examples in the abstract show a 50/50 difference of opinion with regard to cholecystectomy, tonsillectomy and adenoidectomy and cataract extractions, so that the patient might be forgiven if he believed that when he went to a surgeon, he might just as well flip a coin to decide what he should do. We all know that the patient in the real-life situation, of course, has a bias, either pro or con, and it modifies both his voluntary seeking of second opinions and his tendency to ignore the advice, even when two surgeons agree that an operation should be done.

In other words, a certain number of patients are seeking to be persuaded against operation, and if they do not get such advice, they still refuse to have the operation. In contrast, some patients do not want more advice, but they are constrained by programs like the Prudential "second option" program, and they will lose some of their financial benefits if they refuse one of two things, either to have a second opinion or to agree with the second opinion if it advises against operation.

The voluntary utilization of these programs is low, between 1 and 2%. In the Department of Health, Education and Welfare program, with its free telephone line—so called hot line—the utilization in the first six months of the program was about thirty calls a day. In the second phase of the program, that is, calls to the so-called list holders, calls were down to twenty a day. That is on a total national basis.

In the ongoing exchange of opinion between the American College of Surgeons and HEW, some of it public, the latest statement from the Health Care Financing Administration was that the program is a success because the utilization is high. Well, there have been 4500 calls on the hot line in the last six months, and if 67,000 physicians have agreed to participate, these consultants are not going to be very busy.

What worries me is my initial concern that the work of Dr. Zuidema and his colleagues will be misquoted.

I have here something from which I shall read two lines. It is the Moss Committee Subcommittee Report. In this report, Mr. Moss says, "The Subcommittee will utilize the six categories of unnecessary surgery developed by Dr. George Zuidema and presented in his testimony before the Committee." And three pages later they say, "Dr. Zuidema testified that the SOSSUS study, as previously mentioned, identified six categories of unnecessary surgery."

Of course, SOSSUS did nothing of the sort, but George is not alone in being misquoted. An HEW response to an article of mine in *Cancer* says, "Unnecessary surgery estimates have run as high as 30%. Additionally, according to the studies cited by Dr. Hanlon, there are disagreement rates of up to 20% among physicians on appropriate patient treatment."

HEW is really taking a rate of disagreement among physicians, as L. M. Koran did in his 1975 studies in the *New England Journal of Medicine*, and using that disagreement to signify "unnecessary surgery." Then they add this disagreement rate to itself.

DR. CHARLES K. MCSHERRY: (New York, New York): Much of the impetus for this study was provided by material presented at this meeting last year, related to the second opinion surgical program as conducted at Cornell University. The nonconfirmation rate of patients seeking opinions prior to elective operations continues to run in the range of 25–30%. In seeking a cause for what all of us perceive as an inordinately high rate of disagreement among presumably well-qualified surgeons, it is logical to examine in detail the phenomenon of the surgical decision.

Ben Eiseman recently described surgical decisions as "the epitome of decision-making under uncertainty." He further defined surgical judgment as "decision-making under uncertainty, based on past experience." To those of us who have participated in the second opinion programs, the figures described by Dr. Rutkow for lack of agreement regarding the necessity for operation, based upon the surgical case histories, is not surprising. The question that must be answered is: Does the study presented today provide us with an explanation for the high rate of nonconfirmation in the second opinion programs?

I believe the answer to this is a qualified yes. In their manuscript, the authors recognize the limitations of their study, particularly as they relate to the fact that the consultant does not have the opportunity to examine the patient, but only to review a printed summary of their history, physical examination, and laboratory data. In this respect, the yes/no decision is different from the decision arrived at by the second opinion consultant; but despite this limitation, the study does provide us with insight into the surgical decision-making process.

It would be of considerable interest to know what the authors believed or perceived to be the correct response to their test cases. It is difficult to know the true meaning of the yes/no response without having the authors' interpretation as to the appropriate management of these cases.

The study to date with respect to the second opinion program, and now the reliability of the surgical decision-making process, suggests to me that for the sake of completeness it will be necessary to perform one additional study, namely, an evaluation of the patient's perception of his illness. In the second opinion programs, 20% of patients not confirmed for elective operations choose to undergo operations despite the nonconfirmation by the consultant. In addition, 10% of patients whose need for an operation is confirmed choose not to undergo surgical treatment. To understand further the validity of the second opinion program, the next study must focus on the patient. It would appear that the patient's perception of his illness and its effect on his life style and longevity is also critical to the eventual outcome of the second opinion program. Perhaps at that point we may finally resolve the question as to the importance and role of the second opinion programs.

The present study regarding surgical decision-making has implications beyond second opinion programs. The validity of peer review as an effective means of quality assurance must also be scrutinized in the light of the present study by Dr. Rutkow. Perhaps an even more important implication concerns the mechanism of board certification. Since the qualifying examination of the American Board of Surgery is largely based on patient management problems, one must wonder what the reliability of the answers to these problems is in light of the disagreement that exists between equally qualified surgeons. Do the authors feel it necessary to establish some form of baseline control as to the validity of questions used in the surgical examination process?

Finally, we might also reappraise the teaching methods currently used. Dr. Rutkow's data can be interpreted as support for the increasing use of algorithms as an effective learning technique for teaching patient skills and patient management. Perhaps there is yet a place for the cookbook approach to clinical medicine.

DR. FRANK C. SPENCER (New York, New York): I appreciate the opportunity to study this timely and significant paper in some detail and recommend its careful study by all surgeons. As President Beahrs stated yesterday, unless surgeons provide leadership in this socioeconomic area, an abundance of nonsurgeons will gladly tell us what to do.

This is no fairy tale. By coincidence, in the past two weeks the chairmen of the departments of surgery in the universities in New York, with astonishment and grave concern, have been preparing a response to a proposal by the State Health Planning Commission, composed almost completely of nonsurgeons, as President Beahrs predicted. The proposal is to reduce reimbursement to hospitals with surgical residency programs. The object is to reduce the number of surgeons, and hence the cost of medical care, a rationale "based upon the widespread frequency of unnecessary surgery and needless deaths amply demonstrated in reports by *The New York Times* and other publications!"

This report clearly demonstrates in a scientific, randomized manner that variation in clinical judgment is an integral part of medicine. This variation, of course, is the basis for encouraging consultation with uncertain problems, long recognized as an integral part of good surgical care. For brevity, I shall mention only three significant points, some of which have been alluded to by Dr. Hanlon and Dr. McSherry.

The most important, and Dr. Rutkow mentioned this briefly, is that variation in opinion was unrelated to surgical background, especially the method of payment. It made no difference whether the physician was on a fee for service, a capitation, or some other method of payment. What is beautifully demonstrated in this scientific report is that the variation was the same. So the accusation about the economic incentive is well refuted by this paper with good, firm data.

As others have mentioned, there were no direct patient contacts or discussions between physicians, so it may well be that with the variation in patients' personalities, there would be even a wider range of genuine differences. For example, someone with one of these protocols who was disabled and unable to work would have one surgical opinion. If he already had six laparotomy scars, recommendation might be different. So this report may well underestimate the natural variation in clinical practice.

Finally as was shown on one slide, the simple illustration that a total of 21 opinions may be needed to get 95% agreement reduces to absurdity the idea that the second opinion automatically settles the question. Should one have three or four or how many?

For several reasons, I hope this key report is widely read and quoted, not misquoted, as Dr. Hanlon cautions, especially to the lay public. The two popular challenges with which surgeons are regularly assaulted are that many unnecessary operations are done and that a mandatory second opinion will prevent this, thus saving lives and money. A danger is that avoiding operations may neither help the patient nor reduce overall cost. It may simply be an insidious method of rationing health care. Rationing is the simplest way of controlling costs because only a fixed amount of money is budgeted, regardless of need.

One obvious example in the hospital would be to provide all amputees with crutches rather than prostheses. On paper, the hospital budget would be greatly reduced. The influence on quality of life and economic productivity is obvious.

DR. FRANCIS D. MOORE (Boston, Massachusetts): This is an important start in a field that has been well exposed in other areas of human endeavor—in business, in the military, and in game theory. It is still largely unexplored in surgery.

Nevertheless, this paper does present some problems. The fee-for-service incentive, if such exists, may have been completely lost. If the authors would have been willing to offer each recipient a fee of $500 if he answered yes, then we would all believe that such motivation was adequately "controlled."

This paper will be quoted as demonstrating great differences of consultive opinion, but I refer to the actual total of disagreement. Of 28 cases, many carefully built to be confusing, there were actually 12 (all those in the last line of the table, the last two in the bottom two lines, and then three others), in which the agreement was almost universal. Twelve of 28 cases, in some of which the authors were clearly seeking to challenge the system, showed clear agreement. Although these were the "controls," that is the way it is in the real world. Some cases are clear cut. Our totals should include those "reality components."

Some patients have clear problems; others have unclear problems. That is the way it is. That is the way medicine is. That is the way life is. Statistics such as these must include, not exclude, the easy ones.

This spread of views has been "pinned" on surgery. The same thing is true in medicine, pediatrics, psychiatry, and radiology. I would like to tell an illustrative story.

A few years ago a book was written on costs and benefits in surgery, and one chapter was on the history of surgery, telling about some of the ancient operations that had been done that were absolutely pathetic. They had been abandoned. It looked as though surgery was the field that was doing all these foolish things. The authors did not make any mention at all of the fact that there were many periods when diabetes was treated by a ketogenic diet, poliomyelitis was treated by hot pads, and some problems in pediatrics were treated by placing backward children in institutions on the grounds that they were mentally ill.

In viewing behavioral problems as surgeons we must always discipline ourselves to set this in the framework of a broader field. I wish that Dr. Zuidema and his collaborators had included some questions on medicine in their study—questions about the choice to digitalize, the choice to give insulin, a few questions on psychiatry. Should the patient undergo psychoanalysis or shock treatment? Some questions in pediatrics could have been included. What should be done with the mirror writer? What should be done with a congenital anomaly? Should the parents have another child? The authors would have found exactly the same kind of disagreement. It is terribly important for us to realize that point. We should educate the public and legislators to realize that uncertainty is a major feature of the biologic sciences today. It is not limited to surgery.

There is another interesting point. Some legislative committees make a habit of saying that there are 2 to 4 million unnecessary operations per year. It is terribly important when someone says that to nail him down. About 18–20 million operations are performed in the United States each year. Individuals are claiming a 10–20 per cent fraud rate. Just ask them to review the last 100 operations in your hospital and prove it. In that regard tonsillectomy seems to be undergoing an absolutely remarkable change. Tonsillectomy is an operation of which in 1974, when I was being beaten down in one of these committees, I had to admit there had been 1,300,000 performed two years previously. Next year (1980) it appears from the trend that there are going to be less than 350,000. All those national surgical studies and SOSSUS projects seem to have caused at least a part of that improvement.

We have methods of self-correction in this country that are terribly important. They do not all require new Acts of Congress. Some of the uncertainties in this paper are true throughout medicine and throughout the biologic sciences. They are not confined to surgery.

DR. GEORGE D. ZUIDEMA (Closing discussion): I can sympathize with Dr. Hanlon for we have on a number of occasions shared the experience of being misquoted rather extensively.

It is our hope that by showing the opportunities for various interpretations of data, we will be able to demonstrate that perhaps the decision-making process in all of medicine is not quite as precise as the lay public or the press would be given to understand. At any rate, we are sensitive to the points which Dr. Hanlon raised, and we must continue to be alert to those problems as we move on.

I appreciated Dr. McSherry's comments and would simply like to point out that the authors' opinion regarding right or wrong decisions to operate simply did not enter into the process. We were not creating examples which could be entered into with bias but simply taking models based on case histories in which there was an opportunity for a difference of opinion.

As to the question Dr. McSherry raised in terms of the implications as far as the Board examinations and the qualifying examination for the American Board of Surgery, I would point out that there are some differences here in that the patient management portion of that examination is set up in stepwise fashion, so that additional information becomes available to the candidate as he answers his question. This was not true in the vignettes. Such an examination would be an interesting type to pursue, but it is also expensive. Our total budget for this study was less than $600. Obviously the cost of a more extensive approach would have been prohibitive.

We appreciated both Dr. Spencer's and Dr. Moore's points. We were not able to attach a $500 check to this, but we thought we could solve this problem by asking the individuals to serve as second opinion consultants, and therefore they would not be able to perform the operation or to collect a fee.

Second, Dr. Moore pointed out that twelve of the cases in the table had very high levels of agreement. I should point out that eight of the twelve with high agreement were, indeed, controls, and were meant to be set up in that fashion, so that the case histories themselves were not meant to be confusing, but simply to reflect typical cases.

We feel that this is a beginning. We would like to see studies of this kind conducted by other specialties, particularly the medical and pediatric specialties, and we plan to extend studies of this kind to look into some of the other features during the coming year.

Book Reviews

Rhodes Textbook of Surgery (Fifth edition). James D. Hardy (ed.). 2354 pp. Philadelphia, J. B. Lippincott Company, 1977. $38.50.

THE FIFTH EDITION of this surgical textbook is being published seven years after the fourth edition. It has been a popular text and reference since the first edition in 1957 under the editorship of Moyer, Rhodes, Allen and Harkins. The new edition, edited by Dr. James Hardy and titled *Rhodes Textbook of Surgery,* promises to be equally popular. The multitudinous friends and admirers of Jonathan Rhodes will be pleased at the decision of the new editor to give Rhodes name to this book, which is a transition to a greatly expanded, undated and modified format.

This is, indeed, a text for student, graduate trainee and the practicing surgeon. The editor has adopted a problem oriented approach and has enlisted the help of a greatly increased number of contributors each of whom has been chosen because of expertise in a special field. For instance, pediatric surgery has twice the space provided in edition four with 22 contributors, each expert in the problem of his presentation. The same plan is followed throughout the text with the result that one has the feeling of getting the very latest authoritative opinions. Most sections are then followed by an annotated bibliography of important key articles plus a detailed and up to date list of references. For example, one section listed 39 references of which 18 were articles written within the past five years; another section with 88 references included 39 published in 1972 or after. An "overview" by the editor introduces some sections and serves to pull together what might tend to be a disharmonious discourse by multiple authors aiming at the "problem" approach. Any disharmony or lack of cohesiveness is insignificant when compared to the authoritativeness of the more than 300 contributors.

New material in this edition includes sections on immunology of cancer, cardiac resuscitation, respiratory insufficiency and care; expanded sections on renal failure, genetics, and organ transplantation. The completely revised section on fluid and electrolyte disorders is simplified as much as is possible with this complicated subject to the point that the student, resident, and even the practicing surgeon should have no trouble in matching his problem with the help of the tables and examples provided. The special interests of the editor are reflected throughout the text, but especially in the sections on transplantation, the endocrine system, thoracic, gastrointestinal surgery, and cardiac surgery.

The text is generously illustrated and supplemented with photographs, line drawings, and appropriate tables and charts. The book is monumental in size, 2414 pages as compared to 1864 pages in the fourth edition. The increased size was necessary to accomodate the entirely new sections plus the expanded and detailed sections with the multiple contributors of the problem oriented format. In spite of the increased size it was still necessary to omit or sharply curtail some of the sections included in the previous edition. Military surgery is completely omitted as a separate section, orthopedics and fractures is greatly reduced. The specialties of urology, gynecology, neuro- and plastic surgery are excellent but condensed. One volume cannot include everything and the editor has been more than successful in assembling a text that presents surgery as it is in 1978.

For student, resident, or practicing surgeon it is an ideal up-to-date reference for day-to-day problems as well as a means of staying abreast of the rapid advances in all related fields. In these days of such strong and justified emphasis on continuing education the opportunity afforded by a textbook such as this should not be ignored.

EUGENE M. BRICKER, M.D.

Year Book of Cancer—1976. Clark and Cumley (eds.) 582 pages. Chicago, Year Book Publishers. 1976.

THIS IS THE TWENTIETH consecutive annual edition of this monograph by Drs. Clark and Cumley. The format of the 1976 edition is similar to that of past years; the subject matter is arranged in 32 chapters which cover anatomic sites of various tumors and, also, chapters on specific clinical and research disciplines. The senior editors are located at M. D. Anderson Hospital and Tumor Institute, a division of the University of Texas. There are a total of 160 members of the Editorial Board.

The monograph contains abstracts of 296 published cancer papers selected from approximately 17,000 annual publications on oncology appearing in the world's literature. Short comments on the abstract appear at the end of most of the abstracted articles by the reviewing editors. There is also an annotated reference list of related articles at the end of each chapter.

The major thrust of the articles reviewed is clinical, however, there is also included a limited number of abstracts with basic research orientation. The abstracts are presented in an easy readable style. The articles chosen for inclusion represent, in this reviewer's opinion, most of the important advances reported in the oncologic literature in the years 1974 and 1975.

This volume can be recommended as a survey source of the recent oncologic literature for clinical oncologists to update their knowledge in the major areas of clinical cancer and as an introduction to certain new areas of basic cancer research.

WILLIAM W. SHINGLETON, M.D.

Critical Care Medicine: Current Principles and Practices. Max Harry Weil and Herbert Shubin. Hagerstown, Harper and Row.

THIS BOOK IS A COMPILATION of 18 contributions which were originally published in a new section of the *Journal of the American Medical Association*, in which the latest concepts in the field of critical care medicine were reviewed by a variety of authors, many of whom are nationally recognized authorities in their fields. Three additional chapters were added by the original editors of this section, Dr. Max Harry Weil and Dr. Herbert Shubin, who are also the editors of this brief volume of 154 pages. which includes a bibliography of 277 references pertinent to the field.

Chapters one and two, dealing respectively with "the new practice of critical care medicine" and the "guidelines for organization of critical care units" (the latter of which represents the consensus of the Council members of the Society of Critical Care Medicine) present useful material for hospitals considering the establishment of such units. The authors advise against creation of separate facilities with individual administrative and operational identities physically remote from one another in the same hospital, a point with which I heartily agree. Many of the topics covered (such as management of the severely injured patient, ventilatory failure, pulmonary embolism, burns and renal failure) are treated with such brevity as to be of little use to one seeking answers to questions of clinical management in patients with these abnormalities. The hope expressed by the authors that this book will be served as a practical reference for the physician caring for critically ill patients is not realized because of this short coming. However, other chapters (such as those on emergency treatment of cardiac arrythmias, digitalis intoxication and shock associated with barbituate intoxication) are concise summaries which do present practical clinical guidelines to the management of these problems.

In balance, this volume can be recommended as a primer in critical care medicine. For those who deal with the every day problems of intensive care it leaves much to be desired.

JOHN J. SKILLMAN, M.D.

Current Medical Diagnosis and Management. J. Englebert Dunphy and Lawrence W. Way. 1139 pp. Los Altos, Lange Medical Publications. 1977. $16.00.

THIS SURGICAL TEXTBOOK by J. Englebert Dunphy and Lawrence W. Way is different in several ways from the more "standard" textbooks of surgery. First of all, it is paperback and weighs only four pounds, which is one-half the weight of the classical textbooks. Although our students study from a text that has been our choice for many years, I notice that on the wards some of them carry the Dunphy—Way text for ready reference. It does not pretend to be encyclopedic in scope, but bibliographic references at the end of each chapter make additional sources of information readily available. The textbook is divided into 51 chapters, the last 11 of which deal with the surgical specialties and certain surgical diagnostic and therapeutic procedures. The chapter presentations, while brief, give the fundamental material that a medical student should know.

Another attractive feature of this textbook of surgery is that it is updated every two years. This is the third Edition (1977), and the 1st Edition was only published in 1973. While the chapters are essentially the same as the first Edition, as regards content, they are updated with new Concepts of diagnosis and treatment, and the bibliographies are current. Special revision have beenmade in the chapters on surgical nutrition, burns, the thyroid, the spleen, and legal medicine. A new chapter has been added on the diagnostic capabilities of CAT and ultrasound. This reviewer was particularly impressed with Chapter 6 by Jack Nagan, J. D. and Jesse L. Carr, M.D. entitled "Legal Medicine for the Surgeon." This chapter should be required reading for all medical students, residents, and surgical staff. It explains civil and criminal law, and the tort system, in a very lucid manner.

At the end of the book is an appendix that gives normal value tables for the many laboratory tests, a chart for determination of body surface area, and conversion tables to the metric system. This is a very convenient source of data for both medical students and residents. This condensed textbook of surgery has certainly established its place in the education of both the medical student and the surgical resident. For those who have not discovered this fine textbook of surgery, ti is recommended without reservation.

CHESTER B. MCVAY, M.D.

Principles of Surgery. S. Frank Redo. 180 pp. Hagerstown, Harper and Row. 1976. $22.50.

PEDIATRIC SURGERY has made remarkable progress in the last ten years, due to advances in neonatal physiology, application of sophisticated monitoring techniques and improvements in pediatric anesthesia. As a result, the major thrust has been toward performance of definitive operations, rather than temporizing ones, with the expectation of a successful outcome and low mortality. Thus it comes as a disappointment to read a text devoted to surgery in the first six months of life that ignores many of these advances. A text that might have been adequate in 1967 is inadequate ten years later.

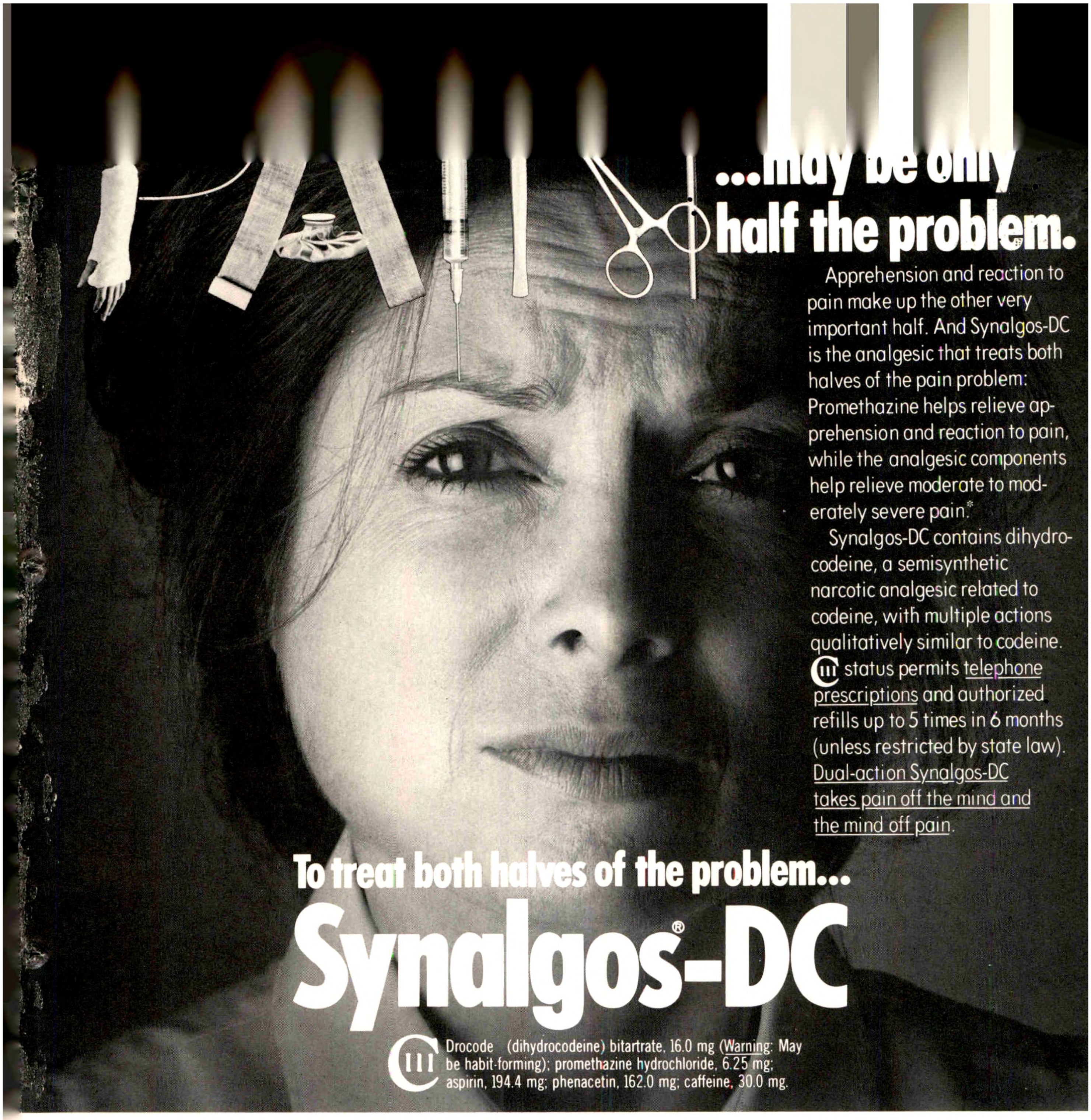
From a physical standpoint, the design and layout of the book is pleasing, easy to read, and well organized. Several chapters are well done, particularly the discussion on newborn physiology by Krauss. The presentations of biliary atresia and necrotizing enterocolitis are detailed and up to date.

Unfortunately, much of the rest of the book is not. Whereas an ileostomy under local anesthesia once was appropriate in operations for intestinal obstruction, today most pediatric surgeons would choose a definitive end-to-end anastomosis, performed under the more optimal conditions of general anesthesia with airway control. The importance of adequate preoperative resuscitation in patients with neonatal intestinal obstruction, including the restoration of cardiac output, is not mentioned. Likewise, the need to excise, or at least tailor, the dilated proximal segment in jejunoileal atresia is ignored. Lacking also is a discussion of the importance of pre-, intra-, and postoperative monitoring of arterial blood gases and osmolality.

Nephrostomy or nephrectomy are no longer acceptable operations in an era when definitive repair, or at the least tubeless diversion, has proved so successful in the management of a wide range of urinary tract disease. The results in Wilms' tumor are far better than those cited by the author: over 50% long-term survival in poor-risk patients, and over 80% in those without metastatic disease.

Neonatal surgery is no longer performed "in life threatening crises only" nor does the pediatric surgeon of today follow the author's advice to "do as little as necessary to save life." A book that does not reflect the current state of the art cannot be recommended.

LUCIAN L. LEAPE, M.D.



...may be only half the problem.

Apprehension and reaction to pain make up the other very important half. And Synalgos-DC is the analgesic that treats both halves of the pain problem: Promethazine helps relieve apprehension and reaction to pain, while the analgesic components help relieve moderate to moderately severe pain.*

Synalgos-DC contains dihydrocodeine, a semisynthetic narcotic analgesic related to codeine, with multiple actions qualitatively similar to codeine. Ⓒ III status permits telephone prescriptions and authorized refills up to 5 times in 6 months (unless restricted by state law). Dual-action Synalgos-DC takes pain off the mind and the mind off pain.

To treat both halves of the problem...

Synalgos®-DC

Ⓒ III Drocode (dihydrocodeine) bitartrate, 16.0 mg (Warning: May be habit-forming); promethazine hydrochloride, 6.25 mg; aspirin, 194.4 mg; phenacetin, 162.0 mg; caffeine, 30.0 mg.

*INDICATIONS: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective for the relief of moderate to moderately severe pain in those situations where the physician wishes to add a mild sedative effect. Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Hypersensitivity to dihydrocodeine, promethazine, aspirin, phenacetin. **WARNINGS:** Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities. **Drug Dependence:** Dihydrocodeine can produce drug dependence of the codeine type and therefore has the potential of being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of dihydrocodeine, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, dihydrocodeine is subject to the provisions of the Federal Controlled Substances Act. **Usage in Ambulatory Patients:** Dihydrocodeine and promethazine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Synalgos-DC should be cautioned accordingly. **Interactions with other Central Nervous System Depressants:** Patients receiving other narcotic analgesics, general anesthetics, other phenothiazines, tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Synalgos-DC may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Patients who have demonstrated a hypersensitivity reaction (e.g. blood dyscrasia, jaundice) with a phenothiazine should not be reexposed to any phenothiazine, including Synalgos-DC, unless in the judgment of the physician the potential benefits of the treatment outweigh the possible hazards. **Usage in Pregnancy:** Reproduction studies have not been performed in animals. There is no adequate information on whether this drug may affect fertility in human males and females or has a teratogenic potential or other adverse effect on the fetus. **Usage in Children:** Since there is no experience in children who have received this drug, safety and efficacy in children have not been established. **PRECAUTIONS:** Phenacetin has been reported to damage kidneys when taken in large amounts for a long time. Promethazine should be administered cautiously to patients with cardiovascular or liver disease. Synalgos-DC should be given with caution to certain patients such as the elderly or debilitated, and those with hypothyroidism, Addison's disease and prostatic hypertrophy and urethral stricture. **ADVERSE REACTIONS:** The most frequently observed reactions include lightheadedness, dizziness, drowsiness, sedation, nausea, vomiting, constipation, pruritus, skin reactions, and rarely, hypotension. **DOSAGE AND ADMINISTRATION:** Dosage should be adjusted according to the severity of the pain and the response of the patient. Synalgos-DC is given orally. The usual adult dose is 2 capsules every 4 hours as needed for pain. **DRUG INTERACTIONS:** The CNS depressant effects of Synalgos-DC may be additive with that of other CNS depressants. See Warnings. Aspirin may enhance the effects of anticoagulants and inhibit the uricosuric effects of uricosuric agents.

Consult direction circular before prescribing.

IVES LABORATORIES INC.
New York, NY 10017
Dedicated to improving the quality of life, through Medicine®
Ives

Save valuable time and gain expert knowledge from these new books

A New Book! **DIAGNOSIS OF ACUTE ABDOMINAL DISEASE.** *By* JOHN M. BEAL, M.D., *and* JOHN G. RAFFENSPERGER, M.D., *both of Northwestern University Medical School, Chicago, Illinois.* Stressing careful observation of the patient and thorough evaluation of presenting signs and symptoms, this new and highly practical book is an important guide in the approach to patients with abdominal problems. It outlines characteristic pain problems through types of presenting diseases—inflammatory diseases, obstructive diseases, perforation, acute abdominal emergencies in the infant, vascular diseases, gynecologic emergencies, etc. This is an important ready reference. *169 pp., 38 illus., charts and tables, paperback, 1979, $9.00.*

A New Book! **SURGICAL CARE: A Physiologic Approach to Clinical Management.** *Edited and with contributions by* ROBERT E. CONDON, M.D., *the Medical College of Wisconsin, Milwaukee; and* JEROME J. DE COSSE, M.D., *Memorial Sloan-Kettering Cancer Center, New York, New York. (47 Contributors).* Focusing on disparate topics of surgical disease, this text provides broad and comprehensive background in selected areas of post-operative care. All subjects are covered in depth and with emphasis on the appropriate mix of biochemical, physiological, pharmacological, and biophysical principles that underlie proper diagnosis and treatment. These principles are translated into the current best methods of management. *About 600 pp. (7¼ x 10¼), illus., October, 1979.*

A New Book! **OUTPATIENT SURGERY.** *Edited and with contributions by* RICHARD CARLTON SCHULTZ, M.D., *University of Illinois at the Medical Center, Abraham Lincoln School of Medicine, Chicago. (25 Contributors).* Doctor Schultz has enlisted the aid of eminent contributors to present this outline and discussion of the practice. The overall objective is to present what is currently acceptable from the standpoint of anesthesia and the major surgical specialties, and to describe how this is done in a modern outpatient setting. The contributors develop herein the essence of what is required to make an outpatient surgical facility function safely, and some of the nuances of what makes it succeed. *About 475 pp. (7 x 10), 342 illus., October 1979.*

A New Book! **PRIMARY CARE OF HAND INJURIES.** *By* WILLIAM L. NEWMEYER, M.D., *University of California, San Francisco.* This book is directed to those physicians who diagnose, treat and refer patients with injuries and afflictions of the hand so that they may reduce disability time and improve final function. The first section is devoted to basic principles common to all hand injuries, and basic principles necessary for treatment. The second section then applies these principles to treatment of specific problems. *297 pp., 215 illus., 1979, $22.50.*

A New Book! **PATHOLOGY OF SOFT TISSUE TUMORS.** *By* STEVEN I. HAJDU, M.D., *Memorial Sloan-Kettering Cancer Center, New York, New York.* Each chapter of this heavily illustrated text features diagnostic and differential diagnostic aspects of soft tissue neoplasms, with special emphasis on the "gray" areas between benign and malignant neoplasms. Embryologic, historical, clinical pathologic, immunological, and ultrastructure aspects are thoroughly discussed. *About 650 pp. (7¼ x 10¼), numerous illus. (several plates in color), tables, October 1979.*

A New Edition! **SURGERY OF THE UPPER RESPIRATORY SYSTEM. Vol. I, 2nd ed.** *By* WILLIAM W. MONTGOMERY, M.D., *Harvard Medical School, Boston, Massachusetts. With contributions by* ALEXANDER S. MACMILLAN, JR., M.D., *and* EDGAR HOLMES, M.D. Step-by-step guidelines for proper diagnosis and treatment of various conditions requiring otolaryngologic surgery are clearly presented in this superior atlas. Emphasized are the most recently developed and unusual operative procedures. *563 pp. (8½ x 11), illus., 1979, $45.00.*

Plan to examine our new books and advance material at the American College of Surgeons meeting in Chicago, Illinois on October 22-25, 1979, Booth 338. If you wish, order directly from us now on 30 days approval.

Use your Master Charge or VISA card to order. Be sure to include your card number and expiration date. Lea & Febiger pays all postage and handling charges on cash and credit card sales.

Lea & Febiger
WASHINGTON SQUARE
PHILADELPHIA, PA./19106

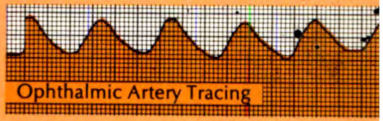
PULSE VOLUME RECORDER (PVR®

The NON-INVASIVE Clinical Vascular Laboratory

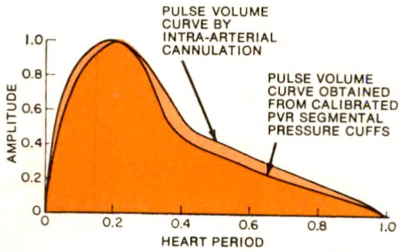
An Extensively Documented Clinical Procedure for the Quantitative Evaluation of Peripheral Vascular Disease:

Arterial — Venous — Cerebral.

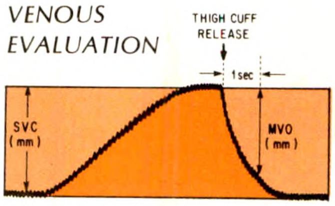
Excellent Long-term Reproducibility and Calibrated Accuracy by Quantitative Segmental Cuff Technique



Ophthalmic artery pressure is rea directly on the OPG Attachment the PVR for the evaluation of collateral circulation to each eye, an its respective cerebral hemisphere



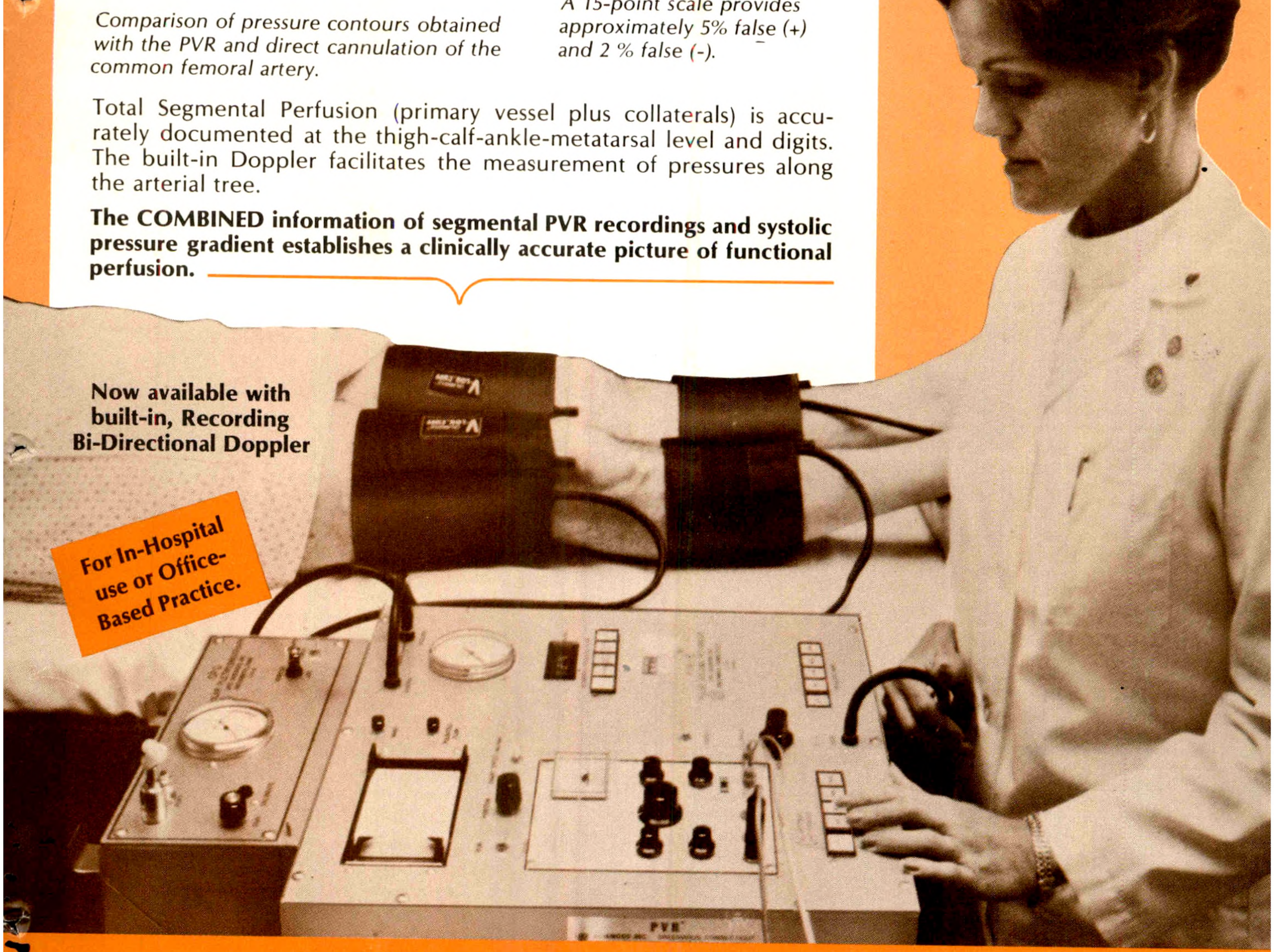
Comparison of pressure contours obtained with the PVR and direct cannulation of the common femoral artery.



A 15-point scale provides approximately 5% false (+) and 2 % false (-).

Total Segmental Perfusion (primary vessel plus collaterals) is accurately documented at the thigh-calf-ankle-metatarsal level and digits. The built-in Doppler facilitates the measurement of pressures along the arterial tree.

The COMBINED information of segmental PVR recordings and systolic pressure gradient establishes a clinically accurate picture of functional perfusion.



Now available with built-in, Recording Bi-Directional Doppler

For In-Hospital use or Office-Based Practice.

Reimbursement for In- and Out-Patients under: Various non-profit hospital and medical-surgical service plans
- Medicare • Veterans Benefits • Commercial Insurance Companies.

* As Developed by The Vascular Laboratory, Dept. of Surgery, Massachusetts General Hospital, Boston, Mass.

References, bibliography, and details on request.

Life Sciences Inc.
270 Greenwich Avenue
Greenwich, Connecticut 06830 U.S
Tel. 203 869-2011

WOUNDS THAT MAKE

CESAREAN SECTION

Postpartum recovery for Mary Edwards was as comfortable as could be expected. After closure, a Non-Adhering *Vaseline® Petrolatum Gauze Dressing* was placed directly over the wound, followed by dry gauze and an outer wrap. Twenty-four hours postsurgery, there was only a normal release of light drainage from the suture line. Because a Non-Adhering Dressing was used between the wound and the dry gauze, there was no sticking during dressing change — no discomfort to the patient.

SPLIT-THICKNESS SKIN GRAFT

Michael Kelly, a volunteer fireman, experienced a severe burn on his left forearm, which required subsequent grafting. To help provide adequate protection of the donor site during healing and to provide mild medication, a Chesebrough-Pond's Non-Adhering *Scarlet Red Ointment Dressing* was placed directly on the wound. During removal, the dressing also helped prevent damage to new tissue growth and further discomfort to the patient. And, for hospital staff, this conveniently prepackaged dressing had an added advantage in that it eliminated the staining and bother of in-hospital preparations.

FACIAL RECONSTRUCTION

Britt Svensson, 18, was involved in an automobile accident during which she sustained several minor facial lacerations, abrasions and a broken nose. Superficial tissue loss was evident, and nose cartilage and overlying skin needed support. Following surgical repair, a protective, Non-Adhering *Xeroform Petrolatum Dressing* was used to help prevent unnecessary loss of tissue fluids, to help prevent disruption of the healing tissue during dressing change, and to maximize patient comfort. Since a Chesebrough-Pond's Non-Adhering Dressing readily conforms to all facial contours — actually clings without sticking — it was of particular value in this repair.

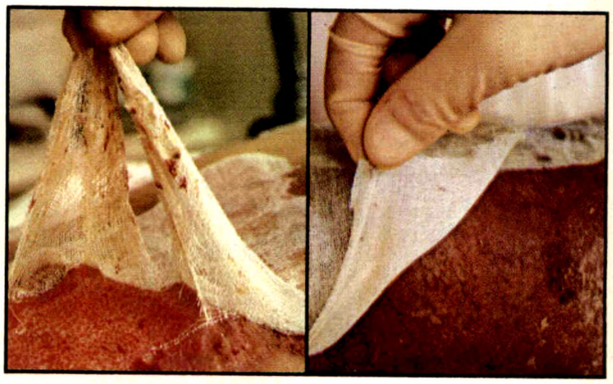
THE BEST DRESSED LIST

APPENDECTOMY

Seven-year-old David Garcia complained of a "bellyache." His doctor's diagnosis of appendicitis was made early, and removal of the appendix followed immediately. All layers of the incision were closed. Drainage was minimal. A mildly medicated, mildly deodorizing, protective dressing —*Xeroform Petrolatum Dressing*—was placed directly on the wound to help prevent unnecessary loss of tissue fluids, and sticking and discomfort to this young patient during dressing changes.

CP Chesebrough-Pond's Inc.
HOSPITAL PRODUCTS DIVISION
GREENWICH, CONNECTICUT 06830

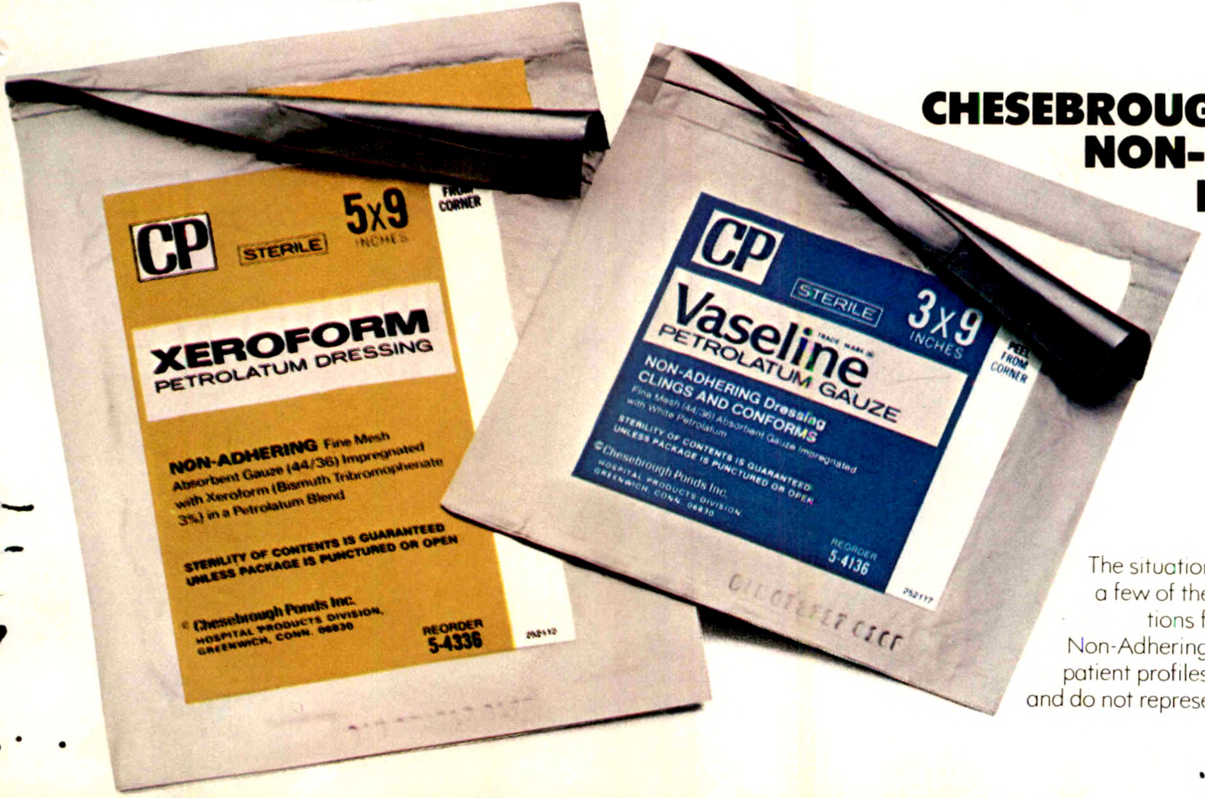
START WITH A GOOD FOUNDATION: A CHESEBROUGH-POND'S NON-ADHERING DRESSING UNDER THE DRY GAUZE



A Chesebrough-Pond's Non-Adhering Dressing next to the wound helps avoid trauma and pain during dressing change. It actually clings without sticking, conforming to all body contours. Dressing removal is easier and more comfortable—wound healing remains undisturbed.

Additionally it helps protect the wound from environmental contamination...helps prevent air and moisture borne contaminants from reaching the wound. Helps prevent unnecessary loss of tissue fluids.

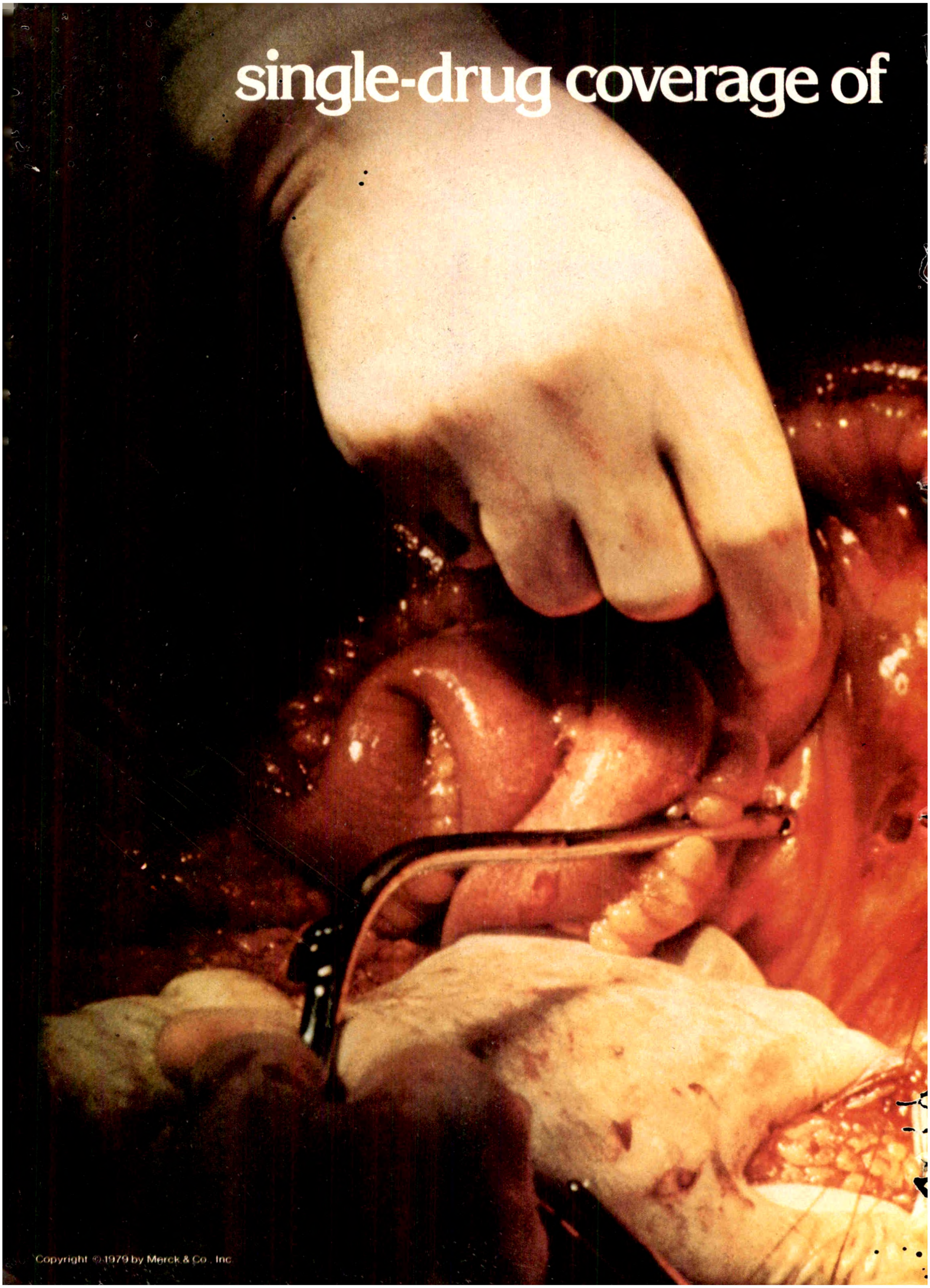
Convenient sizes and packaging; available through surgical supply distributors.


CP
STERILE
5x9 INCHES
PEEL FROM CORNER
XEROFORM
PETROLATUM DRESSING
NON-ADHERING Fine Mesh Absorbent Gauze (44/36) Impregnated with Xeroform (Bismuth Tribromophenate 3%) in a Petrolatum Blend
STERILITY OF CONTENTS IS GUARANTEED UNLESS PACKAGE IS PUNCTURED OR OPEN
© Chesebrough-Ponds Inc.
HOSPITAL PRODUCTS DIVISION, GREENWICH, CONN. 06830
REORDER 5-4336
CP
STERILE
3x9 INCHES
PEEL FROM CORNER
Vaseline
PETROLATUM GAUZE
NON-ADHERING Dressing
CLINGS AND CONFORMS
Fine Mesh (44/36) Absorbent Gauze Impregnated with White Petrolatum
STERILITY OF CONTENTS IS GUARANTEED UNLESS PACKAGE IS PUNCTURED OR OPEN
© Chesebrough-Ponds Inc.
HOSPITAL PRODUCTS DIVISION, GREENWICH, CONN. 06830
REORDER 5-4136

CHESEBROUGH-POND'S NON-ADHERING DRESSINGS

Gentle protection on the healing wound

The situations above represent only a few of the many effective applications for Chesebrough-Pond's Non-Adhering Dressings. Names and patient profiles, however, are fictitious and do not represent actual case histories.



Copyright © 1979 by Merck & Co., Inc.

many mixed infections*

the first cephamycin derivative(1)

Mefoxin® IV/IM

(Cefoxitin Sodium | MSD)

VIALS, containing 1 gram and 2 grams cefoxitin equivalent

a unique profile of:

- spectrum
- efficacy
- safety

*due to susceptible strains of indicated bacteria at indicated sites

(1) MEFOXIN is often referred to as a cephamycin in the scientific literature.

For a brief summary of prescribing information, please see last page of this advertisement.

MSD
MERCK
SHARP&
DOHME

single-drug coverage

spectrum[†]

- Active against most aerobic pathogens—gram-negative as well as gram-positive
- Active against most anaerobic pathogens—including *Bacteroides fragilis*
- Active against most β-lactamase-producing strains that destroy the activity of many cephalosporins and penicillins

Not active against most strains of *Pseudomonas aeruginosa* and enterococci (e.g., *Streptococcus faecalis*) and many strains of *Enterobacter cloacae*. Methicillin-resistant staphylococci are almost uniformly resistant to MEFOXIN® (Cefoxitin Sodium, MSD).

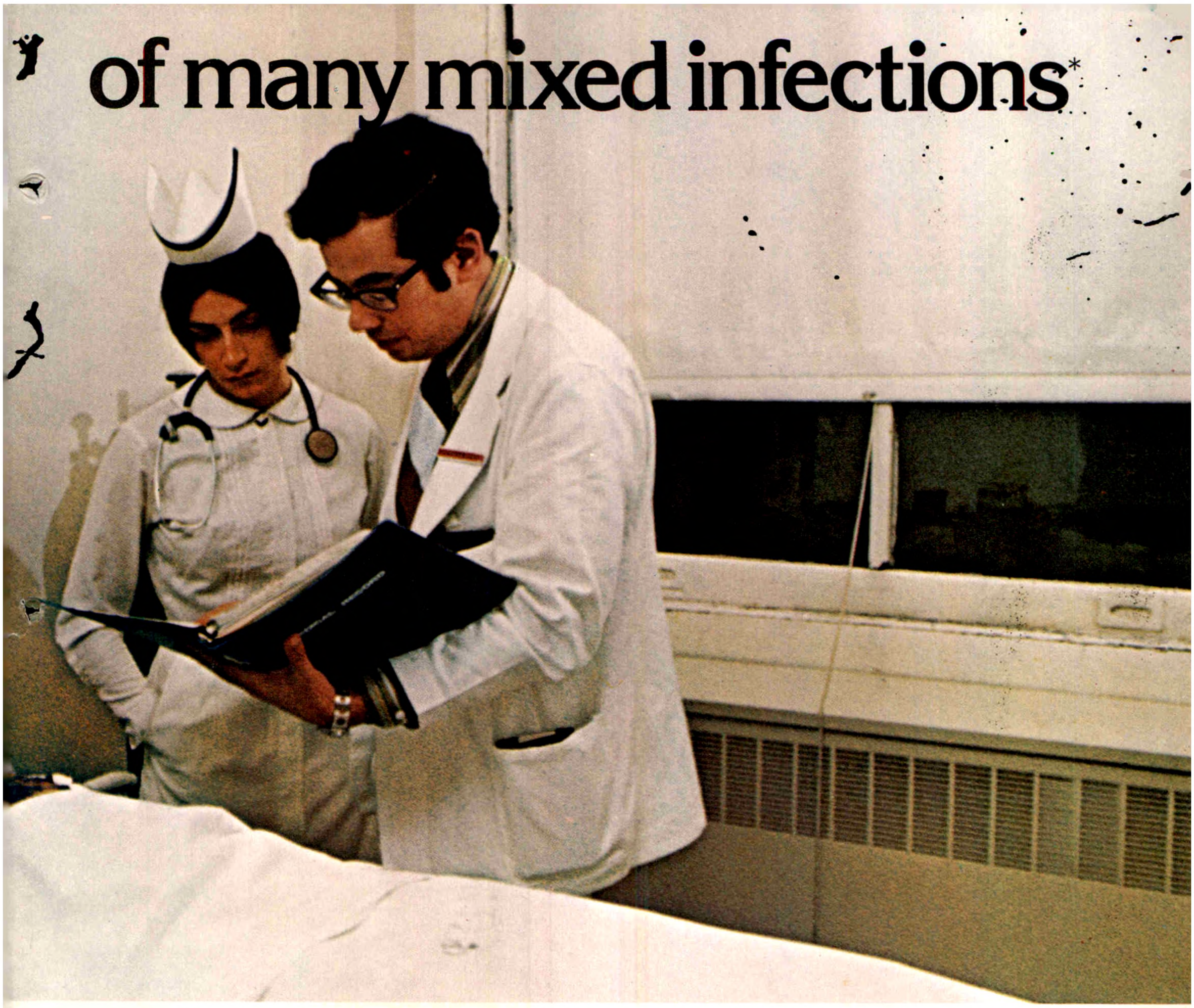
[†] *In vitro* activity does not necessarily imply *in vivo* effectiveness.

efficacy

- In a wide range of infections*—such as:
  - peritonitis
  - intra-abdominal abscess
  - skin and skin structure infections
- In infections caused by single or multiple pathogens

*due to susceptible strains of indicated bacteria at indicated sites

# of many mixed infections*



safety

- Safety comparable to that of cephalothin
- Generally well tolerated, the most common adverse reaction being local reactions following IV or IM injection. Contraindicated in patients who have shown hypersensitivity to cefoxitin and the cephalosporin group of antibiotics. Give with caution to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs.

A SIMPLE AND FAMILIAR DOSAGE REGIMEN

Type of Infection	Usual Daily Dosage	Frequency and Route
Uncomplicated forms‡ of infections such as pneumonia, urinary tract infection, cutaneous infection	3-4 grams	1 gram every 6-8 hours IV or IM
Moderately severe or severe infections	6-8 grams	1 gram every 4 hours or 2 grams every 6-8 hours IV
Infections commonly needing antibiotics in higher dosage (e.g., gas gangrene)	12 grams	2 grams every 4 hours or 3 grams every 6 hours IV

‡including patients in whom bacteremia is absent or unlikely

the first cephamycin derivative

Mefoxin® IV/IM

(Cefoxitin Sodium | MSD)

MSD
MERCK
SHARP &
DOHME

*due to susceptible strains of indicated bacteria at indicated sites

For a brief summary of prescribing information, please see following page.

Mefoxin® IV/IM
(Cefoxitin Sodium | MSD)

Indications: Treatment of serious infections caused by susceptible strains of the designated microorganisms in the following diseases:
LOWER RESPIRATORY TRACT INFECTIONS, including pneumonia and lung abscess, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), other streptococci (excluding enterococci, e.g., *Strep. faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Klebsiella* species, *Hemophilus influenzae*, and *Bacteroides* species.
GENITOURINARY INFECTIONS. Urinary tract infections caused by *E. coli*, *Klebsiella* species, *Proteus mirabilis*, indole-positive *Proteus* (i.e., *P. morganii*, *P. rettgeri*, and *P. vulgaris*), and *Providencia* species. Uncomplicated gonorrhea due to *N. gonorrhoeae*.
INTRA-ABDOMINAL INFECTIONS, including peritonitis and intra-abdominal abscess, caused by *E. coli*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,‡ and *Clostridium* species.
GYNECOLOGICAL INFECTIONS, including endometritis, pelvic cellulitis, and pelvic inflammatory disease, caused by *E. coli*, *N. gonorrhoeae*, *Bacteroides* species including the *B. fragilis* group,‡ *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species, and group B streptococci.
SEPTICEMIA caused by *Strep. pneumoniae* (formerly *D. pneumoniae*), *Staph. aureus* (penicillinase and non-penicillinase producing), *E. coli*, *Klebsiella* species, and *Bacteroides* species including the *B. fragilis* group.‡
BONE AND JOINT INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing).
SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing), *Staph. epidermidis*, streptococci (excluding enterococci, e.g., *Strep. faecalis*), *E. coli*, *P. mirabilis*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,‡ *Clostridium* species, *Peptococcus* species, and *Peptostreptococcus* species.
Although appropriate culture and susceptibility studies should be performed, therapy may be started while awaiting these results. Cefoxitin is not active *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci (e.g., *Strep. faecalis*) and many strains of *Enterobacter cloacae*. Methicillin-resistant staphylococci are almost uniformly resistant to cefoxitin.
Contraindications: Previous hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.
Warnings: BEFORE THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. GIVE WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.
Precautions: The total daily dose should be reduced in patients with transient or persistent reduction of urinary output due to renal insufficiency because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses. As with other antibiotics, prolonged use may result in overgrowth of nonsusceptible organisms; repeated evaluation of the patient's condition is essential. If superinfection occurs, take appropriate measures. Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.
Interference with Laboratory Tests—As with cephalothin, high concentrations (>100 mcg/ml) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction and produce false increases of modest degree in creatinine levels reported; serum samples should not be analyzed for creatinine if withdrawn within 2 hours of cefoxitin administration. A false-positive reaction for glucose in urine has been observed with CLINITEST§ reagent tablets.
Pregnancy—In women of childbearing potential, weigh anticipated benefit against possible risks.
Nursing Mothers—Cefoxitin is excreted in human milk in low concentrations.
Infants and Children—Safety and efficacy in infants and children have not yet been established.
Adverse Reactions: The most common adverse reactions have been local reactions following intravenous or intramuscular injection. Other adverse reactions have been encountered infrequently. *Local Reactions*—Thrombophlebitis with intravenous administration; pain, induration, and tenderness after intramuscular injections. *Allergic Reactions*—Rash, pruritus, eosinophilia, fever, and other allergic reactions. *Gastrointestinal*—Nausea, vomiting, and diarrhea. *Blood*—Transient leukopenia, neutropenia, and hemolytic anemia; a positive direct Coombs test may develop in some individuals, especially those with azotemia. *Liver Function*—Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase. *Renal Function*—Elevations in serum creatinine and/or blood urea nitrogen levels.
Note: In group A beta-hemolytic streptococcal infections, therapy should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated. Intramuscular injections should be well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel.
How Supplied: Sterile cefoxitin sodium in vials and infusion bottles containing 1 gram or 2 grams cefoxitin equivalent.
For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

‡*B. fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*
§Registered trademark of Ames Company, Division of Miles Laboratories, Inc.

MSD
MERCK SHARP & DOHME

J8MF05R2(106)

You can now order article reprints from this publication

University Microfilms International, in cooperation with publishers of this journal, offers a highly convenient Article Reprint Service. Single articles or complete issues can now be obtained in their original size (up to 8½ x 11 inches). For more information please complete and mail the coupon below.

ARTICLE REPRINT SERVICE
University Microfilms International

☐ YES! I would like to know more about the Article Reprint Service. Please send me full details on how I can order.
☐ Please include catalogue of available titles.

Name ____________ Title ____________
Institution/Company ____________
Department ____________
Address ____________
City ____________ State ____________ Zip ____________

Mail to: **University Microfilms International**
Article Reprint Service
300 North Zeeb Road
Ann Arbor, Michigan 48106

"Current abstracts are amplified and illuminated by comments of the members of the Editorial Board, based on their own clinical experiences as well as those of other recognized authorities" . . . just one of the reasons why Lippincott's

Current Surgery

Formerly REVIEW OF SURGERY

Editor: Lloyd M. Nyhus, M.D.

Associate Editors: Robert E. Condon, M.D.,
W. G. Schenk, Jr., M.D., Seymour Schwartz, M.D.

helps Resident (special rate only **$16.00**) and Veteran Surgeon alike to keep up with current progress, trends, and attitudes in all branches of surgery and the surgical specialties.

A true saver of precious reading time—from its detailed Contents Pages to its meaty reviews, and abstracts especially classified for reader convenience—a typical issue includes:

- Focus—several Reviews of timely or other special significance
- An original Report of major importance
- Twenty or more Abstracts with Commentary (and oft-times, rebuttal)
- Residents Corner—comprising Brief (1 to 3-page) Reports and Investigations
- In-depth Reviews of Current Books in Surgery

TO PUT THE BIMONTHLY CURRENT SURGERY AT YOUR FINGERTIPS NOW,

SUBSCRIBE TODAY . . .

J. B. LIPPINCOTT COMPANY. East Washington Square. Philadelphia. Pa. 19105 AS 9/79

Please enter my subscription to CURRENT SURGERY for 1 year (6 issues), at ☐ **$20** (U.S.); ☐ **$24** (all other countries); Resident Rate ☐ **$16** (U.S. only; also note "year" of residency and Specialty ____________________).

PLEASE PRINT

Name ____________________

Address ____________________

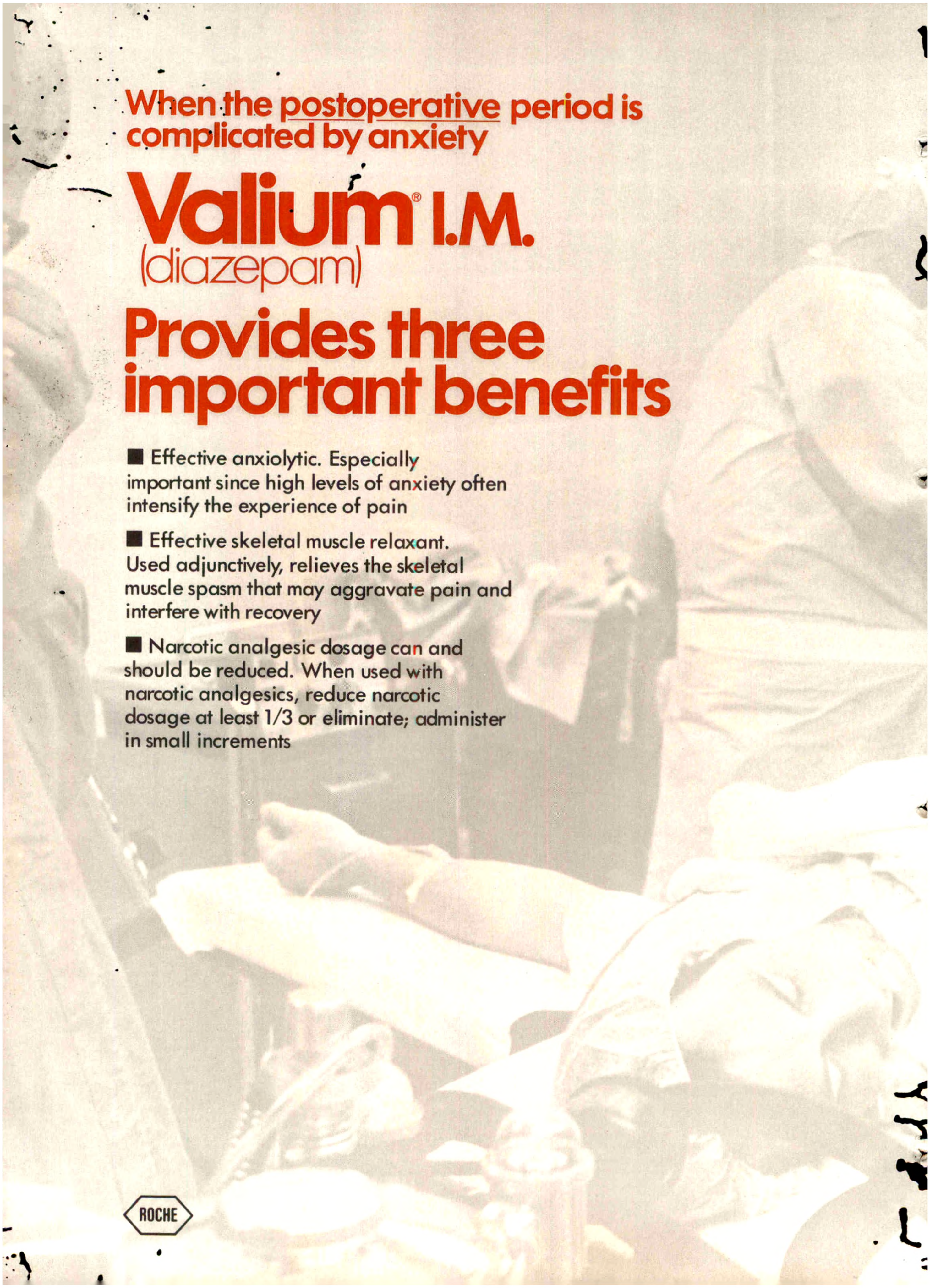
City/State/Zip ____________________

☐ Payment Enclosed.

☐ Charge my account.

My Specialty is:

____



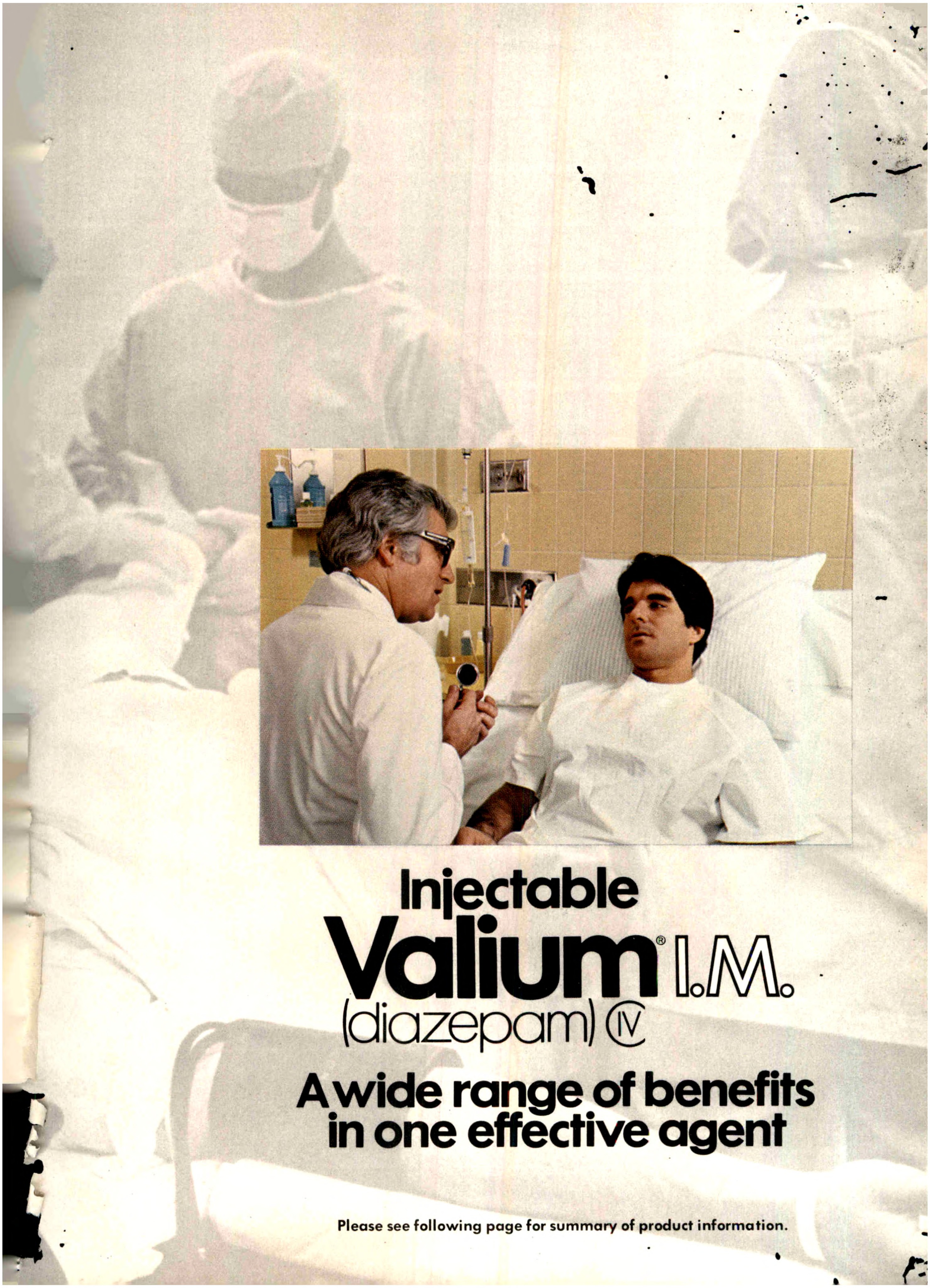
When the postoperative period is complicated by anxiety

Valium® I.M.
(diazepam)

Provides three important benefits

- Effective anxiolytic. Especially important since high levels of anxiety often intensify the experience of pain
- Effective skeletal muscle relaxant. Used adjunctively, relieves the skeletal muscle spasm that may aggravate pain and interfere with recovery
- Narcotic analgesic dosage can and should be reduced. When used with narcotic analgesics, reduce narcotic dosage at least 1/3 or eliminate; administer in small increments

ROCHE



Injectable

Valium® I.M.

(diazepam) Ⓒ IV

A wide range of benefits in one effective agent

Please see following page for summary of product information.

Injectable
Valium® I.M.
(diazepam) Ⓒ IV

can help the surgical patient every step of the way

☐ promptly controls anxiety/tension before and after surgery
☐ diminishes pain-related anxiety
☐ narcotic analgesic dosage can and should be reduced

ready-to-use 2-ml Tel-E-Ject® disposable syringes, 2-ml ampuls, 10-ml vials — 5 mg/ml

Please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.,* operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms (similar to those with barbiturates, alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal/muscle cramps, vomiting, sweating). Keep addiction-prone individuals under careful surveillance because of predisposition to habituation/dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy.

If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), *i.e.,* phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium (diazepam) directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, *administer I.V. slowly;* for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

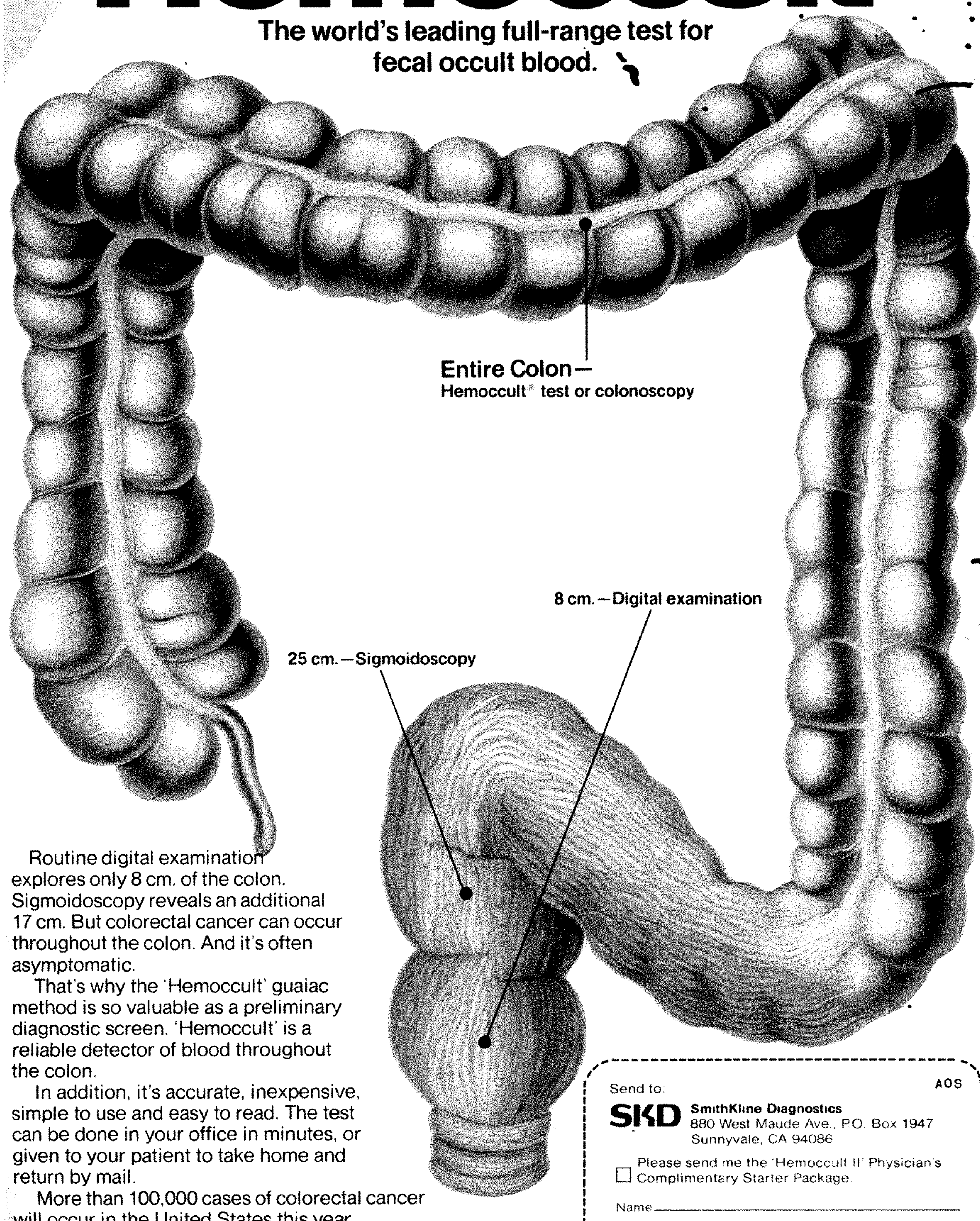
Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

ROCHE
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Hemoccult®

The world's leading full-range test for fecal occult blood.



Routine digital examination explores only 8 cm. of the colon. Sigmoidoscopy reveals an additional 17 cm. But colorectal cancer can occur throughout the colon. And it's often asymptomatic.

That's why the 'Hemoccult' guaiac method is so valuable as a preliminary diagnostic screen. 'Hemoccult' is a reliable detector of blood throughout the colon.

In addition, it's accurate, inexpensive, simple to use and easy to read. The test can be done in your office in minutes, or given to your patient to take home and return by mail.

More than 100,000 cases of colorectal cancer will occur in the United States this year. The earlier they are diagnosed, the greater the chances for successful treatment. Send for your free 'Hemoccult' starter package, today.

'Hemoccult' is available through local distributors, nationwide.

Send to: AOS

SKD **SmithKline Diagnostics**
880 West Maude Ave., P.O. Box 1947
Sunnyvale, CA 94086

☐ Please send me the 'Hemoccult II' Physician's Complimentary Starter Package.

Name ______________________________

Address ______________________________

City ______________ State ______________ Zip ______

Phone ______________________________

Surgical Oncology Fellowships at NIH

The Surgery Branch of the National Cancer Institute, National Institutes of Health, Public Health Service, is offering a limited number of two-year Fellowship (Clinical Associate) positions to outstanding candidates who have completed at least two years of residency training in surgery.

The surgical oncology training program consists of six to eight months of primary clinical responsibility for surgical patients on the wards of the Clinical Center of the National Institutes of Health. The remaining time is spent in full-time laboratory research. A third year of continued research experience is provided for selected surgical Fellows. Emphasis is placed on a broad multi-disciplinary view of cancer management and in an intensive laboratory research experience.

Trainees who qualify for the Commissioned Corps, U.S. Public Health Service, have a starting salary of $21,600 with a variety of additional benefits plus a substantial bonus in the third year. Moving and travel expenses are paid and health care is free for Commissioned Corps. Comparable civilian fellowships are also available. Positions begin on July 1, 1981, 1982. For further information and for application procedures, contact:

Dr. Steven A. Rosenberg
Chief, Surgery Branch
National Cancer Institute
National Institutes of Health
Public Health Service
Bldg. 10, Room 10N116
Bethesda, MD 20205
Telephone: (301) 496-4164

An NIH Associate Program

An Equal Opportunity Employer

SECOND EDITION

■

Illustrated Preoperative and Postoperative Care

■

By Philip Thorek, M.D., F.A.C.S., F.I.C.S
Illustrated by Carl Linden

Relying on the use of original illustrations coupled with succinct, on-target text, this second edition of *Illustrated Preoperative and Postoperative Care* is a masterful exposition of Dr. Thorek's rich personal experience.

Practicality is the theme as Dr. Thorek covers evaluation of the surgical patient, the immediate post-op period, the recovery room, use of fluid and electrolytes, chemotherapy, and surgical complications. The chapter on surgical pharmacology, new to this edition, includes the concepts of alpha and beta stimulators and blockers as they pertain to the therapeutic value of various drugs.

The beautiful illustrations support the text admirably, and in many cases are fully explanatory in themselves.

"*. . . a useful reference source for neophyte or experienced surgeon alike.*"—Military Medicine

"*. . . invaluable to any student, surgeon, resident, intern or clerk, who ever intends to do surgery of any type.*"—International Surgery.

147 Pages • 79 Illus. • 2nd Edition, 1973 • $12.00

Lippincott

J. B. Lippincott Company
East Washington Square • Phila., Pa. 19105

Please send me:

☐ ILLUSTRATED PREOPERATIVE AND POSTOPERATIVE CARE $12.00

Name ______

Address ______

City ______ State ______ Zip ______

☐ Payment enclosed Save postage & handling ☐ Charge and bill me Plus postage & handling

Also available at your medical bookstore AS 9/79

INDEX TO ADVERTISERS

PHARMACEUTICAL SUPPLIES

Boehringer Ingelheim Limited
  Dulcolax 11A
Breon Laboratories, Inc.
  Marcaine 28A,29A
Bristol Laboratories
  Cefadyl .... 50A thru 52A
  Kantrex 68A,69A
Burroughs Wellcome Company
  Neosporin Topicals .... Cover IV
Carnation Company
  Instant Breakfast 47A
Eaton Laboratories
  Vivonex 8A,9A
Endo Laboratories
  Nubain .... 33A thru 38A
  Percodan 26A,27A
  Percocet-5 .... 62A,63A
Flint Laboratories
  Travase 25A
Ives Laboratories
  Synalgos 75A
Knoll Pharmaceuticals
  Dilaudid .... Cover II
  Vicodin .... 18A thru 20A
Eli Lilly & Company
  Keflin 59A,60A
  Nebcin .... 22A thru 24A
McNeil Laboratories
  Tylox 13A
Mead Johnson Pharmaceutical Division
  Colace 21A
  Cytoxan .... 14A thru 16A
  Megace .... 43A thru 46A
  Sustacal 32A
Merck Sharp & Dohme
  Mefoxin .... 80A thru 84A
Organon Pharmaceuticals
  Deca Durabolin 70A,71A
Parke Davis & Company
  Chloromycetin .... 4A thru 6A
Roche Laboratories
  Valium Injectable .... 86A thru 88A
Roche Products, Inc.
  Dalmane .... 72A thru 74A
Roerig
  Geopen .... 92A,Cover III
Searle Laboratories
  Metamucil 58A
Smith Kline & French Laboratories
  Ancef 30A,31A
USV Laboratories
  MVI 56A,57A

SUPPLIES & EQUIPMENT

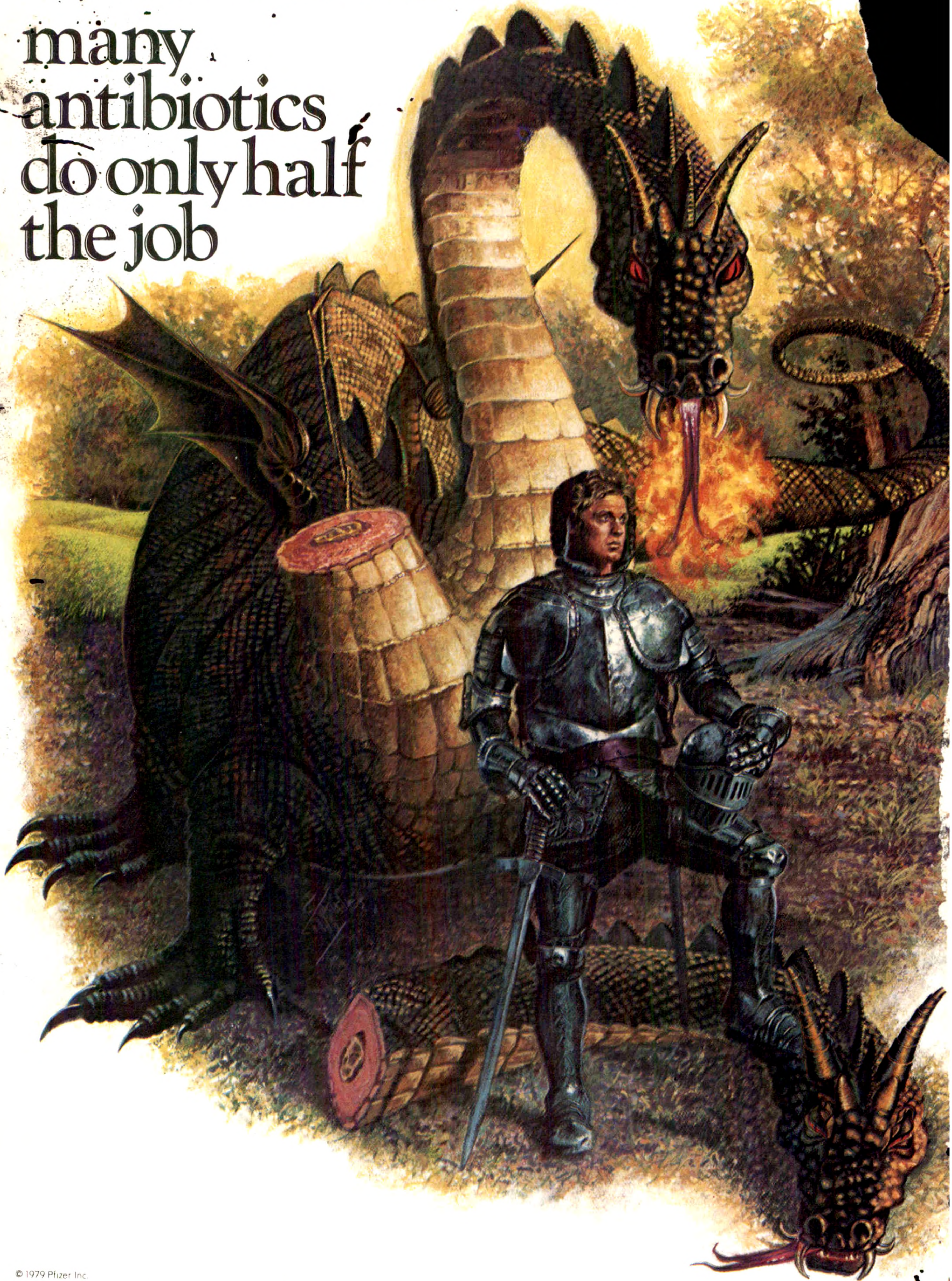
American Cystoscope Makers, Inc.
  Sigmoidoscope 1A
American Optical
  Short Colonscope 39A
Chesebrough Pond's
  Non Adhering Dressings 78A,79A
Ethicon, Inc.
  Control Release Needle Suture 17A
  Vicryl Sutures 64A,65A
Johnson & Johnson
  Dermicel & Dermilite II 66A,67A
Life Sciences, Inc.
  Pulse Volume Recorder 77A
  Vascular Diagnostic Computer 55A
Narco Pilling
  Surgical Instruments 48A
Ortho Diagnostics
  Chromogenic Assay III 53A
The Purdue Frederick Company
  Betadine Surgical Products 2A
Reed & Carnrick
  Cortifoam 40A,41A
Smith Kline Diagnostics
  Hemmocult 89A

MISCELLANEOUS

American College of Surgeons 49A
American Society of Maxillofacial
  Surgeons 61A
Cook County School of Medicine 61A
Harper & Row Publishers 56A
Jessie Jones Box Corporation 62A
Lea & Febiger 76A
J. B. Lippincott Company 20A,26A,58A
  60A,65A,68A,85A,90A
Mount Sinai School of Medicine 61A
National Institute of Health 90A
W. B. Saunders Company 42A
Springer Verlag 54A
United States Public Health
  Service Hospital 61A
Xerox University Microfilms
  International 84A

IN MIXED ANAEROBIC/AEROBIC INFECTIONS

many antibiotics do only half the job



© 1979 Pfizer Inc.

combat both anaerobes* and gram-negative aerobes* with one antibiotic

GEOPEN® IM/IV

(CARBENICILLIN DISODIUM)

1-gm, 2-gm, 5-gm, and 10-gm vials and 30-gm Bulk Pharmacy Package

Indications: Primarily for treatment of infections due to susceptible strains of *Pseudomonas aeruginosa*, *Proteus* species (particularly indole-positive strains), and certain *Escherichia coli*.

Clinical effectiveness has been demonstrated in the following infections when due to these organisms: Severe systemic infections and septicemia, including meningitis due to *Hemophilus influenzae* and *Streptococcus pneumoniae*; genitourinary tract infections including those due to *Neisseria gonorrhoeae*, *Enterobacter*, and *S. faecalis* (enterococcus); acute and chronic respiratory infections (though clinical improvement has been shown, bacteriologic cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis); soft-tissue infections. Also indicated in the following infections due to susceptible anaerobic bacteria: Septicemia; lower respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, pelvic inflammatory disease, pelvic abscess and salpingitis; skin and soft-tissue infections.

Although indicated primarily in gram-negative infections, activity against gram-positive organisms should be kept in mind when both gram-positive and gram-negative organisms are isolated (see **Actions**).

In infections due to certain susceptible strains of *Ps. aeruginosa*, clinical efficacy may be enhanced by combined therapy with gentamicin sulfate in full therapeutic dosages (see gentamicin sulfate package insert).

NOTE: During therapy sensitivity testing should be repeated frequently to detect the possible emergence of resistant organisms.

Actions: Organisms found to be susceptible *in vitro* include: GRAM-NEGATIVE ORGANISMS—*Ps. aeruginosa*, *Proteus mirabilis*, *Pr. morgani*, *Pr. rettgeri*, *Pr. vulgaris*, *E. coli*, *Enterobacter* spp, *Salmonella* spp, *H. influenzae*, *Neisseria* spp, *Bacteroides* spp, and *Fusobacterium* spp.
GRAM-POSITIVE ORGANISMS—*Staphylococcus aureus* (non-penicillinase producing), *Staph. albus*, *S. pneumoniae*, beta-hemolytic streptococci, *S. faecalis*, *Clostridium* spp, *Peptococcus* spp, and *Peptostreptococcus* spp.

In vitro synergism between Geopen (carbenicillin disodium) and gentamicin sulfate has been demonstrated for certain strains of *Ps. aeruginosa*.

Some newly emerging pathogenic strains of *Herellea*, *Mima*, *Citrobacter*, and *Serratia* have also shown *in vitro* susceptibility.

Not stable in the presence of penicillinase. Most *Klebsiella* species are resistant. Some strains of *Pseudomonas* have developed resistance fairly rapidly.

Contraindications: Known penicillin allergy.

Warnings: Serious and occasional fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

Observe patients with renal impairment for bleeding manifestations and adhere strictly to dosage recommendations; if bleeding manifestations appear, discontinue antibiotic and institute appropriate therapy.

Individuals with history of penicillin hypersensitivity reactions have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, appropriate therapy should be instituted and discontinuance of carbenicillin therapy considered, unless the infection is life threatening and only amenable to carbenicillin therapy. The usual agents (antihistamines, pressor amines, and corticosteroids) should be readily available.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Precautions: As with any other potent agent, it is advisable to check periodically for organ-system dysfunction, including renal, hepatic, and hematopoietic systems, during prolonged therapy. Emergence of resistant organisms, such as *Klebsiella* spp and *Serratia* spp, which may cause superinfection, should be kept in mind. Each gram contains 4.7 mEq sodium; in patients where sodium restriction is necessary, such as cardiac patients, periodic electrolyte determinations and monitoring of cardiac status should be made. In a few patients receiving high doses, hypokalemia has been reported; periodic serum potassium determinations should be made and corrective measures should be implemented when necessary. As with any penicillin preparation, an allergic response, including anaphylaxis, may occur, particularly in a hypersensitive individual. Cases of gonorrhea with a suspected primary lesion of syphilis should have darkfield examinations before treatment. In all other cases where concomitant syphilis is suspected, monthly serological tests should be made for a minimum of 4 months.

Intramuscular injections should be made well within the body of a relatively large muscle (not into the lower and mid-third of the upper arm), and aspiration is necessary to help avoid inadvertent injection into a blood vessel. Intravenous infusion should be given as slowly as possible. Reconstituted solution should be discarded after 24 hours if stored at room temperature, after 72 hours if refrigerated. **Reconstituted Bulk Pharmacy Package solution should not be used for direct infusion.** The maximum recommended dose is 40 gm per day; intramuscular injections should not exceed 2 gm per injection.

Adverse Reactions: *Hypersensitivity Reactions*— Skin rashes, pruritus, urticaria, drug fever, and anaphylactic reactions. *Gastrointestinal Disturbances*— Nausea. *Hemic and Lymphatic Systems*— Anemia, thrombocytopenia, leukopenia, neutropenia, and eosinophilia. *Blood, Hepatic, and Renal Studies*— SGOT and SGPT elevations have been observed, particularly in children. To date, no clinical manifestations of hepatic or renal disorders have been demonstrated. *CNS*— Convulsions or neuromuscular irritability could occur with excessively high serum levels. *Other*— Pain at the site of injection, rarely accompanied by induration; in uremic patients receiving high doses (24 gm/day), hemorrhagic manifestations associated with abnormalities of coagulation tests, such as clotting and prothrombin time. *Vein Irritation and Phlebitis*— Particularly when undiluted solution is injected directly into the vein.

How Supplied: Available in 1-gm, 2-gm, and 5-gm vials for IM/IV use; 2-gm, 5-gm, and 10-gm Piggyback Units for IV use; and 30-gm Bulk Pharmacy Package.

For Full Prescribing Information, please see package insert.

ROERIG Pfizer

A division of Pfizer Pharmaceuticals, New York, New York 10017

---

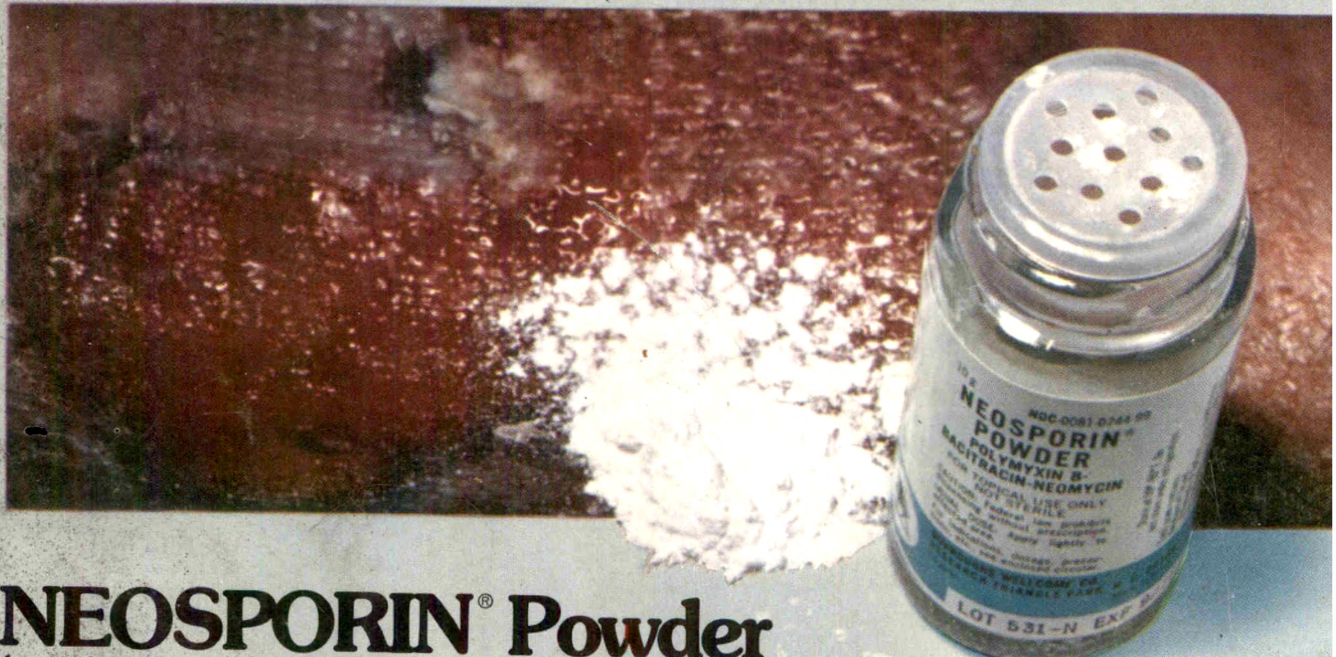
ptible strains of indicated organisms at indicated sites

DRY THERAPY
for moist, oozing lesions

Powder. In shaker-top vials. Especially useful in the treatment of suppurating or serous discharging lesions, infected ulcers, moist or oozing lesions, and intertriginous areas.*

A combination of three antibiotics with a spectrum of action encompassing virtually all pathogenic bacteria found topically. And, since these antibiotics a seldom used systemically, the patient is spared sensitization to those antibiotics which might later be required systemically.

Famous Neosporin® (polymyxin B-bacitracin-neomycin) therapy. In convenient powder form.



NEOSPORIN® Powder
(polymyxin B-bacitracin-neomycin)

NEOSPORIN® POWDER
POLYMYXIN B-BACITRACIN-NEOMYCIN
FOR TOPICAL USE ONLY (NOT STERILE)

DESCRIPTION: Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 Units; zinc bacitracin 400 Units; neomycin sulfate (equivalent to 3.5 mg neomycin base) 5 mg; in a special lactose base.

***INDICATIONS:** Based on a review of this drug by the National Academy of Sciences — National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: For topical administration for the treatment of the listed localized infections or for suppressive therapy in such conditions:
Prophylactic: Postoperative and traumatic surface wounds, biopsy sites, skin grafts and donor sites, dermabrasion.
Therapeutic (when infected by susceptible organisms): Vascular ulcers, decubitus ulcers, pyodermas, infected eczemas, infected dermatoses.
Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

PRECAUTIONS: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs. It is to be noted that the powder is not intended for sterile use in surgical procedures such as those involving abdominal or thoracic body cavities.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

DOSAGE AND ADMINISTRATION: Apply lightly to the area to be treated as often as needed; treatment area may be covered with a dressing or left exposed, as desired. In biopsy sites, dermabraded areas, etc., the powder may be mixed with a little powdered gelatin foam to provide concurrent hemostasis.

SUPPLIED: Shaker-top vial of 10 g
NDC 0081-0744-99.

Complete literature available on request from Professional Services Dept. PML.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709